

The normal maintenance downtime for STN will be extended on December 15. STN will be unavailable beginning Saturday, December 15, at 17:00 U.S. Eastern Standard Time until Sunday, December 16, at 01:00.

The normal schedule for STN maintenance downtime (22:00 to 01:00) will resume on December 22.

* * * * *

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* * * * * STN Columbus * * * * *

FILE 'HOME' ENTERED AT 08:32:22 ON 14 DEC 2007

=> file reg

COST IN U.S. DOLLARS

SINCE FILE

TOTAL

ENTRY

SESSION

FULL ESTIMATED COST

0.21

0.21

FILE 'REGISTRY' ENTERED AT 08:32:33 ON 14 DEC 2007

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Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 13 DEC 2007 HIGHEST RN 957969-84-5

DICTIONARY FILE UPDATES: 13 DEC 2007 HIGHEST RN 957969-84-5

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH June 29, 2007

Please note that search-term pricing does apply when conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

<http://www.cas.org/support/stngen/stndoc/properties.html>

=>Testing the current file.... screen

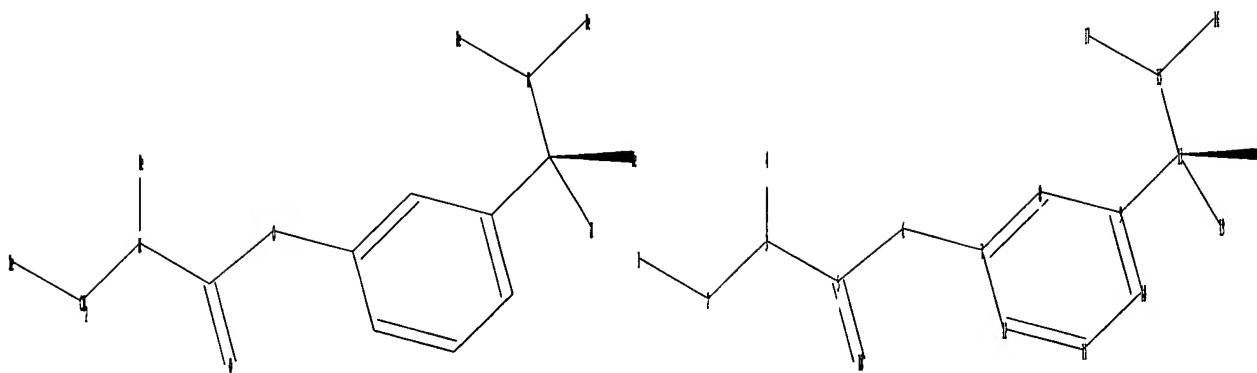
ENTER SCREEN EXPRESSION OR (END):end

=> screen 964

L1 SCREEN CREATED

=>

Uploading C:\Program Files\Stnexp\Queries\10523927clm.str



```

chain nodes :
1  2  3  4  5  6  13  14  15  16  17  18  19
ring nodes :
7  8  9  10  11  12
chain bonds :
1-2  2-3  3-4  3-5  5-6  5-18  6-7  9-13  13-14  13-15  13-19  15-16  15-17
ring bonds :
7-8  7-12  8-9  9-10  10-11  11-12
exact/norm bonds :
3-5  5-6  5-18  6-7  13-15
exact bonds :
1-2  2-3  3-4  9-13  13-14  13-19  15-16  15-17
normalized bonds :
7-8  7-12  8-9  9-10  10-11  11-12

```

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Match level :
1:Atom  2:Atom  3:Atom  4:Atom  5:Atom  6:Atom  7:CLASS  8:CLASS  9:CLASS  10:CLASS
11:CLASS 12:CLASS 13:Atom 14:Atom 15:Atom 16:Atom 17:Atom 18:Atom 19:Atom

```

Stereo Bonds:

14-13 (Single Wedge).

Stereo Chiral Centers:

13 (Parity=Don't Care)

Stereo RSS Sets:

Type=Relative (Default). 1 Nodes= 13

L2 STRUCTURE UPLOADED

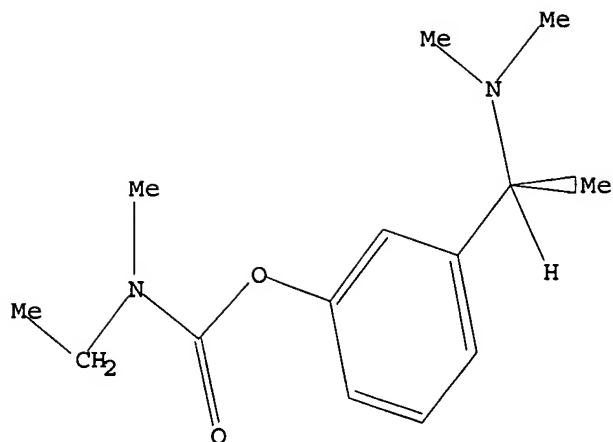
=> que L2 AND L1

L3 QUE L2 AND L1

=> d L2

L2 HAS NO ANSWERS

L2 STR



Structure attributes must be viewed using STN Express query preparation.

=> s L2 full

FULL SEARCH INITIATED 08:33:05 FILE 'REGISTRY'

FULL SCREEN SEARCH COMPLETED - 173 TO ITERATE

100.0% PROCESSED 173 ITERATIONS
SEARCH TIME: 00.00.01

18 ANSWERS

L4 18 SEA SSS FUL L2

=> file caplus

COST IN U.S. DOLLARS

SINCE FILE

TOTAL

ENTRY

SESSION

FULL ESTIMATED COST

172.10

172.31

FILE 'CAPLUS' ENTERED AT 08:33:10 ON 14 DEC 2007

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FILE COVERS 1907 - 14 Dec 2007 VOL 147 ISS 26

FILE LAST UPDATED: 13 Dec 2007 (20071213/ED)

Effective October 17, 2005, revised CAS Information Use Policies apply. They are available for your review at:

<http://www.cas.org/infopolicy.html>

=> s L4

L5 603 L4

=> s hydrogen tartarate

1032532 HYDROGEN
 6104 HYDROGENS
 1035925 HYDROGEN
 (HYDROGEN OR HYDROGENS)
 656 TARTARATE
 33 TARTARATES
 685 TARTARATE
 (TARTARATE OR TARTARATES)
 L6 4 HYDROGEN TARTARATE
 (HYDROGEN(W) TARTARATE)

=> s L5 (w) L6
 L7 0 L5 (W) L6

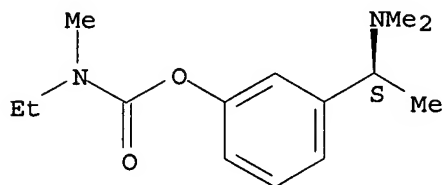
=> s L5 and L6
 L8 1 L5 AND L6

=> d L8 bib abs hitstr

L8 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2007 ACS on STN
 AN 2005:503344 CAPLUS
 DN 143:120709
 TI A validated chiral liquid chromatographic method for the enantiomeric separation of Rivastigmine hydrogen tartarate, a cholinesterase inhibitor
 AU Srinivasu, M. K.; Rao, B. Mallikarjuna; Reddy, B. Shyam Sundar; Kumar, P. Rajeneder; Chandrasekhar, K. B.; Mohakhud, Pradeep K.
 CS Analytical Research, Custom Pharmaceutical Services, Dr. Reddy's Laboratories, Hyderabad, 500049, India
 SO Journal of Pharmaceutical and Biomedical Analysis (2005), 38(2), 320-325
 CODEN: JPBADA; ISSN: 0731-7085
 PB Elsevier B.V.
 DT Journal
 LA English
 AB A new and accurate chiral liquid chromatog. method was developed for the enantiomeric resolution of Rivastigmine hydrogen tartrate, (-)-S-N-ethyl-3-[(1-dimethyl-amino)ethyl]-N-methylphenyl-carbamate hydrogen tartrate, a cholinesterase inhibitor in bulk drugs. The enantiomers of Rivastigmine hydrogen tartrate were baseline resolved on a Chiralcel OD-H (250 mm + 4.6 mm, 5 µm) column using a mobile phase system containing hexane: isopropanol: trifluoroacetic acid (80:20:0.2, volume/volume/v). The resolution between the enantiomers was not less than 4 and interestingly distomer was eluted prior to eutomer in the developed method. The presence of trifluoroacetic acid in the mobile phase has played an important role in enhancing chromatog. efficiency and resolution between the enantiomers. The developed method was extensively validated and proved to be robust. The limit of detection and limit of quantification of (R)-enantiomer were found to be 500 and 1500 ng/mL, resp. for 10 µl injection volume. The percentage recovery of (R)-enantiomer was ranged from 95.2 to 104.3 in bulk drug samples of Rivastigmine hydrogen tartrate. Rivastigmine hydrogen tartrate sample solution and mobile phase were found to be stable for at least 48 h. The proposed method was found to be suitable and accurate for the quant. determination of (R)-enantiomer in bulk drugs. Chiralcel OJ-H column can also be used as an alternative for the above purpose.
 IT 129101-54-8, Rivastigmine hydrogen tartrate 415973-05-6, (R)-Rivastigmine
 RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
 (enantiomeric separation of Rivastigmine hydrogen tartrate by HPLC)
 RN 129101-54-8 CAPLUS
 CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester, (2R,3R)-2,3-dihydroxybutanedioate (1:1) (CA INDEX NAME)

CRN 123441-03-2
CMF C14 H22 N2 O2

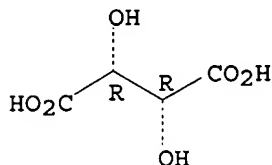
Absolute stereochemistry. Rotation (-).



CM 2

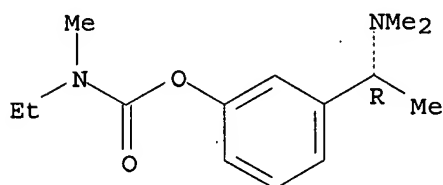
CRN 87-69-4
CMF C4 H6 O6

Absolute stereochemistry.



RN 415973-05-6 CAPLUS
CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1R)-1-(dimethylamino)ethyl]phenyl
ester (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> s process
2536922 PROCESS
1727961 PROCESSES
L9 3782401 PROCESS
(PROCESS OR PROCESSES)

=> s L9 and L5
L10 33 L9 AND L5

=> d L10 1-33 bib abs hitstr

L10 ANSWER 1 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2007:1116285 CAPLUS
DN 147:427355
TI Preparation of phenothiazine derivatives for treatment of tauopathy

IN Wischik, Claude Michel; Rickard, Janet Elizabeth; Harrington, Charles Robert; Horsley, David; Storey, John Mervyn David; Marshall, Colin; Sinclair, James Peter
 PA Wista Laboratories Ltd., Singapore
 SO PCT Int. Appl., 49pp.
 CODEN: PIXXD2
 DT Patent
 LA English
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2007110630	A1	20071004	WO 2007-GB1107	20070328
	W:				
	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
	RW:				
	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				

PRAI US 2006-786699P P 20060329

AB This invention pertains to processes for the preparation of phenothiazine derivs. for the treatment of tauopathy, such as Alzheimer's disease. For example, 3-ethylaniline was reacted with Et iodide for N,N-diethyl-3-ethylaniline, which was treated with sodium nitrite in hydrochloric acid, and then with iron fillings in hydrochloric acid to obtain N4,N4,2-triethyl-1,4-benzenediamine dihydrochloride. The intermediate obtained above was treated with sodium sulfide, and then iron (III) chloride in water to give 3,7-bis(diethylamino)-1,9-diethyl-phenothiazin-5-ium chloride as a final product. The product obtained above showed inhibitory activity against tau protein aggregation in an in vitro assay with the concentration required to inhibit 50% of the tau-tau binding

as $3.7 \pm 0.5 \mu\text{M}$.

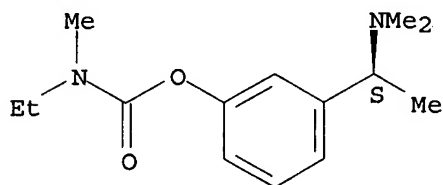
IT 123441-03-2, Rivastigmine

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (co-drug; preparation of phenothiazine derivs. for treatment of tauopathy)

RN 123441-03-2 CAPLUS

CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 2 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN

AN 2007:993697 CAPLUS

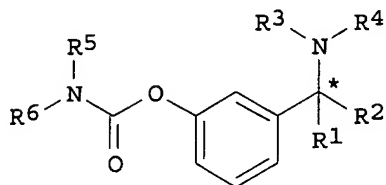
DN 147:343798

TI Process for the preparation of carbamic acid
 3-(aminoalkyl)phenyl esters

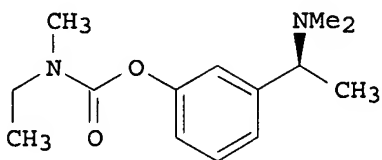
IN Wang, Zhi-Xian; Horne, Stephen E.; Murthy, K. S. Keshava

PA Can.
 SO U.S. Pat. Appl. Publ., 6pp.
 CODEN: USXXCO
 DT Patent
 LA English
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2007207990	A1	20070906	US 2006-365596	20060302
	WO 2007098573	A1	20070907	WO 2007-CA253	20070228
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
PRAI	US 2006-365596	A	20060302		
OS	CASREACT 147:343798; MARPAT 147:343798				
GI					



I



II

AB A process for the preparation of carbamic acid 3-(aminoalkyl)phenyl esters I [wherein R1, R2 independently = H or alkyl; R3, R4 independently = alkyl; R5, R6 independently = H or alkyl; R3 and R4, R5 and R6 together with the nitrogen to which they are attached form a cyclic three to eight membered ring, with or without a heteroatom like nitrogen or oxygen, resp.; the carbon center designated "*" can be racemic or enantiomerically enriched in the (R)- or (S)-configuration] and pharmaceutically acceptable acid addition salts thereof is disclosed. As an example, (S)-Rivastigime II was synthesized with >99.0% ee via treatment of the corresponding phenol with 1,1'-carbonyldiimidazole in acetonitrile followed by condensation with N-ethylmethylamine.

IT 123441-03-2P

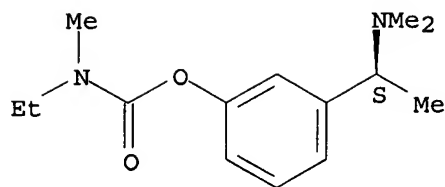
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)

(preparation of carbamic acid (aminoalkyl)phenyl esters via carbamoylation of (aminoalkyl)phenols, carbonylating agents and amines)

RN 123441-03-2 CAPLUS

CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L10 ANSWER 3 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN

AN 2007:986010 CAPLUS

DN 147:439300

TI Molecular pathology and pharmacogenomics in Alzheimer's disease: polygenic-related effects of multifactorial treatments on cognition, anxiety, and depression

AU Cacabelos, Ramon

CS EuroEspes Biomedical Research Center, Institute for CNS Disorders, Coruna, Spain

SO Methods and Findings in Experimental and Clinical Pharmacology (2007), 29(Suppl. A), 1-91

CODEN: MFEPDX; ISSN: 0379-0355

PB Prous Science

DT Journal; General Review

LA English

AB A review. Alzheimer's disease (AD) is a major problem of health in developed societies together with cardiovascular disorders and cancer. The lack of accurate diagnostic markers for early prediction and an effective therapy are the two most important problems to efficiently halt disease progression. The pharmacol. treatment in AD accounts for 10-20% of direct costs, and less than 20% of AD patients are moderate responders to conventional drugs (donepezil, rivastigmine, galantamine, memantine), with doubtful cost-effectiveness. The neuropathol. hallmark of AD (amyloid deposition in senile plaques, neurofibrillary tangle formation, and neuronal loss) are both the phenotypic expression of a pathogenic process in which more than 200 genes and their products are potentially involved. Drug metabolism, and the mechanisms underlying drug efficacy and safety, are also genetically regulated complex traits in which hundreds of genes cooperatively participate. Structural and functional genomics studies demonstrate that genomic factors, probably induced by environmental factors, cerebrovascular dysfunction, and epigenetic phenomena, might be responsible for AD pathogenic events leading to premature neuronal death. The AD population exhibits a higher genetic variation rate than the control population, with absolute and relative genetic variations of 40-60% and 0.85-1.89%, resp. AD patients also differ in their genomic architecture from patients with other forms of dementia. Functional genomics studies in AD reveal that age of onset, brain atrophy, cerebrovascular hemodynamics, brain bio-elec. activity, cognitive decline, apoptosis, immune function, lipid metabolism dyshomeostasis, and amyloid deposition are associated with AD-related genes. Pioneering pharmacogenomics studies also demonstrate that the therapeutic response in AD is genotype-specific, with APOE-4/4 carriers as the worst responders to conventional treatments. About 10-20% of Caucasians are carriers of defective CYP2D6 polymorphic variants that alter the metabolism and effects of AD drugs and many psychotropic agents currently administered to patients with dementia. There is a moderate accumulation of AD-related genetic variants of risk in CYP2D6 poor metabolizers and ultra-rapid metabolizers, which are the worst responders to conventional drugs. With diverse multifactorial therapies, combining different types of drugs and metabolic factors, it is partially possible to slowdown cognitive deterioration, improving non-cognitive symptoms, such as anxiety and depression, which currently aggravate cognition and increase the difficulties in disease management: however, the association of the APOE-4 allele with specific genetic variants of other genes (e.g., CYP2D6, ACE)

neg. modulate the therapeutic response to multifactorial treatments affecting cognition, mood and behavior. Pharmacogenetic and pharmacogenomic factors may account for 60-90% of drug variability in drug disposition and pharmacodynamics. The incorporation of pharmacogenetic/pharmacogenomic protocols to AD research and clin. practice can foster therapeutics optimization by helping to develop cost-effective pharmaceuticals and improving drug efficacy and safety.

IT 123441-03-2, Rivastigmine

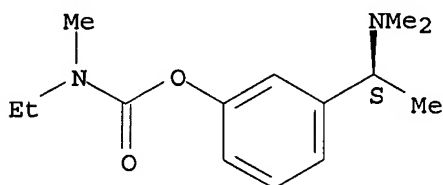
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(donepezil, rivastigmine, galantamine and memantine were used in patient with Alzheimer's disease)

RN 123441-03-2 CAPLUS

CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RE.CNT 684 THERE ARE 684 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 4 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN

AN 2007:919756 CAPLUS

DN 147:322710

TI Process for preparation of N-ethyl-N-methylaminoformic acid
3-[1-(methylamino)ethyl]phenyl ester as intermediate of rivastigmine

IN Tang, Zhaojun; Fu, Xiaoming

PA Hangzhou Shengmei Medicine Technology Development Co., Ltd., Peop. Rep. China

SO Faming Zhuanli Shenqing Gongkai Shuomingshu, 12pp.

CODEN: CNXXEV

DT Patent

LA Chinese

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	CN 101016257	A	20070815	CN 2007-10067343	20070214
PRAI	CN 2007-10067343		20070214		

AB This invention pertains to a method for producing N-ethyl-N-methylaminoformic acid 3-[1-(methylamino)ethyl]phenyl ester. The compound is applied as intermediate of rivastigmine for treating Alzheimer's disease. The preparation method has the advantages of high product yield and quality, low cost, and simple operation.

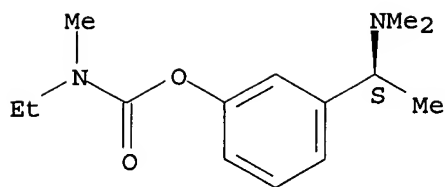
IT 123441-03-2P

RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of N-ethyl-N-methylaminoformic acid
3-[1-(methylamino)ethyl]phenyl ester as intermediate of rivastigmine)

RN 123441-03-2 CAPLUS

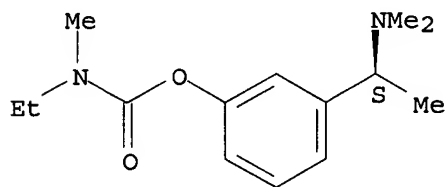
CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



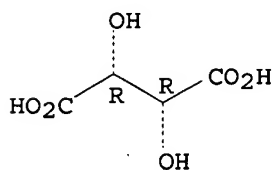
IT 129101-54-8P
 RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP
 (Preparation)
 (preparation of N-ethyl-N-methylaminoformic acid 3-[1-(methylamino)ethyl]phenyl ester as intermediate of rivastigmine)
 RN 129101-54-8 CAPLUS
 CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl
 ester, (2R,3R)-2,3-dihydroxybutanedioate (1:1) (CA INDEX NAME)
 CM 1
 CRN 123441-03-2
 CMF C14 H22 N2 O2

Absolute stereochemistry. Rotation (-).



CM 2
 CRN 87-69-4
 CMF C4 H6 O6

Absolute stereochemistry.



L10 ANSWER 5 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN
 AN 2007:609363 CAPLUS
 DN 147:39157
 TI Transdermal therapeutic systems providing specific plasma concentrations
 of active ingredients, such as cholinesterase inhibitors
 IN Gargiulo, Paul M.; Lane, Roger Michael; Wall, Bettina; Platt, Beatrix;
 Theobald, Frank
 PA Novartis AG, Switz.; LTS Lohmann Therapie-Systeme AG
 SO Can. Pat. Appl., 37pp.
 CODEN: CPXXEB
 DT Patent
 LA English
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	CA 2563110	A1	20070601	CA 2006-2563110	20061010
	US 2007128263	A1	20070607	US 2006-539979	20061010
	WO 2007064407	A1	20070607	WO 2006-US39557	20061010
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				

PRAI US 2005-741511P P 20051201

AB The present invention relates to a transdermal therapeutic system (TTS) with improved compliance, adhesion, tolerability and/or safety that provides specific plasma concns. of an active agent, e.g., a cholinesterase inhibitor. The TTS comprises (a) a backing layer, (b) a reservoir (matrix) layer containing one or more active ingredients and one or more polymers, and (c) a silicone adhesive layer containing a silicone polymer and a tackifier. The TTS comprises an addnl. detachable protective layer. A process of manufacturing and use of the TTS are also described. Thus, a bilayer TTS was produced comprising (i) a polymer matrix layer containing rivastigmine 30.0%, acrylic adhesive Durotak 387-2353 49.9%, acrylate polymer Plastold B 20.0%, and vitamin E 0.1%, and (ii) a silicone adhesive layer containing Bio-PSA Q7-4302 98.9%, silicone oil 1.0%, and vitamin E 0.1%. The saturation solubility of rivastigmine in the silicone adhesive

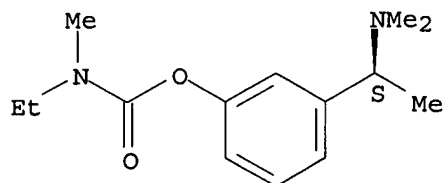
was about 5% by weight. The pharmacokinetic study in patients with Alzheimer's disease showed that the inter-patient variability of rivastigmine was lower after patch as compared to the oral administration. Also, improved pharmacol. properties of the patch compared with a capsule formulation were observed.

IT 123441-03-2, Rivastigmine
 RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (controlled-release transdermal therapeutic system comprising polymeric matrix and silicone adhesive)

RN 123441-03-2 CAPLUS

CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



IT 129101-54-8, Rivastigmine hydrogen tartrate
 RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (controlled-release transdermal therapeutic system comprising polymeric matrix and silicone adhesive)

RN 129101-54-8 CAPLUS

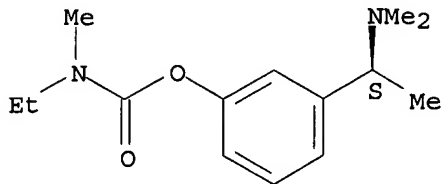
CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester, (2R,3R)-2,3-dihydroxybutanedioate (1:1) (CA INDEX NAME)

CM 1

CRN 123441-03-2

CMF C14 H22 N2 O2

Absolute stereochemistry. Rotation (-).

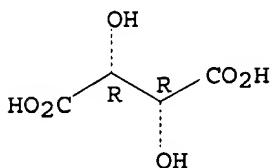


CM 2

CRN 87-69-4

CMF C4 H6 O6

Absolute stereochemistry.



L10 ANSWER 6 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN

AN 2007:545009 CAPLUS

DN 147:30831

TI Synthesis of rivastigmine

IN Chen, Weimin; Feng, Jin; Sun, Pinghua

PA Jinan University, Peop. Rep. China

SO Faming Zhuanli Shenqing Gongkai Shuomingshu, 7pp.

CODEN: CNXXEV

DT Patent

LA Chinese

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	CN 1962624	A	20070516	CN 2006-10123473	20061110
PRAI	CN 2006-10123473		20061110		

OS CASREACT 147:30831

AB The chemical name of rivastigmine is (S)-N-ethyl-3-[(1-dimethylamino)acryl]-N-methyl-carbamate Ph ester. The title method comprises the steps of: (1) performing a reaction of m-hydroxyacetophenone with N,N-dimethylformamide at a mol. ratio of 1:(4-800), 155-170°C and normal pressure for 5-24 h to obtain 3-[1-(dimethylamino)ethyl]phenol, and (2) esterifying with methylethylaminoformyl chloride at a mol. ratio of 1:1.05 to obtain rivastigmine. The method is environment-friendly, and has the advantages of simple process, convenient and safe operation, wide raw material resources, and little pollution.

IT 123441-03-2P, Rivastigmine

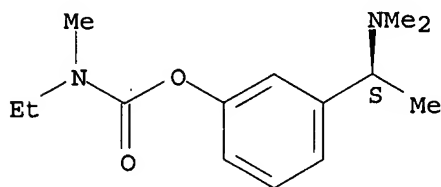
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(synthesis of rivastigmine)

RN 123441-03-2 CAPLUS

CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl

ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L10 ANSWER 7 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN

AN 2007:397779 CAPLUS

DN 147:541597

TI Process for the preparation of rivastigmine

IN Parekh, Nayan Ratilal; Patil, Dhananjay Pandit

PA Torrent Pharmaceuticals Ltd., India

SO Indian Pat. Appl., 42pp.

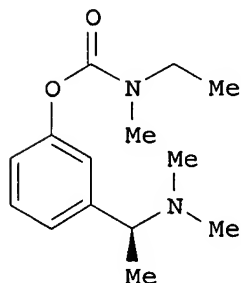
CODEN: INXXBQ

DT Patent

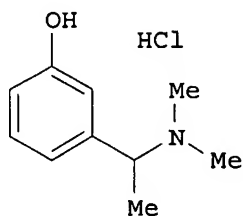
LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	IN 2004MU00682	A	20060616	IN 2004-MU682	20040625
PRAI	IN 2004-MU682		20040625		
GI					



I



II

AB The invention relates to a process for the preparation of the (2R,3R)-tartrate salt of rivastigmine (I), which is a carbamate-type reversible cholinesterase inhibitor. Rivastigmine is used for the treatment of the cognitive, functional, and behavioral symptoms of Alzheimer's disease. The process of the invention avoids the use of expensive and/or hazardous reagents such as sodium cyanoborohydride and sodium hydride, and provides a higher yield of the final product. The target compound may be prepared according to the process of the invention as shown by the following example. Reductive amination of 3-hydroxyacetophenone with dimethylamine in the presence of sodium borohydride and titanium(IV) isopropoxide gave amine II in 36% yield. The amine underwent carbamate formation with N-ethyl-N-methylcarbamoyl chloride in the presence of potassium hydroxide in DMSO to form racemic rivastigmine in 99% yield. Diastereomeric salt resolution of rivastigmine followed by liberation of the free base and salt formation with (R,R)-tartaric acid gave the tartrate salt of I in 6.5% overall yield.

IT 399515-02-7P

RL: IMF (Industrial manufacture); PUR (Purification or recovery); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(chiral intermediate; process for the preparation of rivastigmine)

RN 399515-02-7 CAPLUS

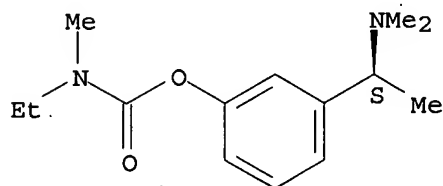
CN Butanedioic acid, 2,3-bis[(4-methylbenzoyl)oxy]-, (2S,3S)-, compd. with
3-[(1S)-1-(dimethylamino)ethyl]phenyl ethylmethylcarbamate (1:1) (9CI)
(CA INDEX NAME)

CM 1

CRN 123441-03-2

CMF C14 H22 N2 O2

Absolute stereochemistry. Rotation (-).

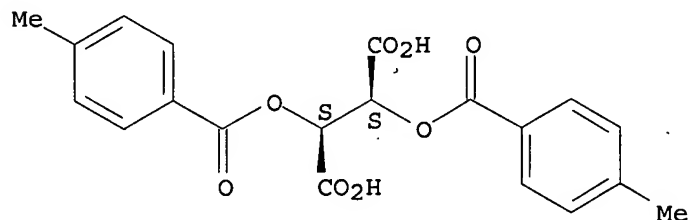


CM 2

CRN 32634-68-7

CMF C20 H18 O8

Absolute stereochemistry. Rotation (+).



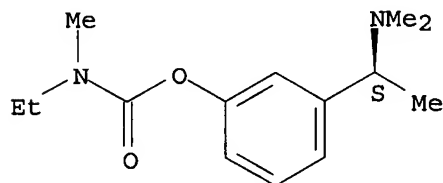
IT 123441-03-2P

RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic
preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; process for the preparation of rivastigmine)

RN 123441-03-2 CAPLUS

CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl
ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



IT 129101-54-8P, Rivastigmine tartrate

RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP
(Preparation)
(target compound; process for the preparation of rivastigmine)

RN 129101-54-8 CAPLUS

CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl

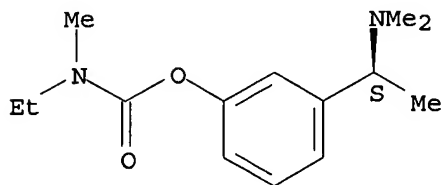
ester, (2R,3R)-2,3-dihydroxybutanedioate (1:1) (CA INDEX NAME)

CM 1

CRN 123441-03-2

CMF C14 H22 N2 O2

Absolute stereochemistry. Rotation (-).

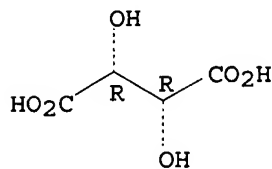


CM 2

CRN 87-69-4

CMF C4 H6 O6

Absolute stereochemistry.



L10 ANSWER 8 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN

AN 2007:257897 CAPLUS

DN 146:295621

TI Process for preparation of rivastigmine and tartrate

IN Ma, Dawei; Pan, Qiangbiao; Pan, Song

PA Shanghai Aobo Bio-Pharmaceutical Technology Co., Ltd, Peop. Rep. China;
Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences;
Zhejiang Huahai Pharmaceutical Co., Ltd.

SO PCT Int. Appl., 27pp.

CODEN: PIXXD2

DT Patent

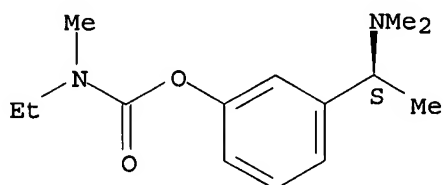
LA Chinese

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2007025481	A1	20070308	WO 2006-CN2246	20060901
	W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW			
	RW:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
	CN 1923801	A	20070307	CN 2005-10029393	20050902
PRAI	CN 2005-10029393	A	20050902		

OS CASREACT 146:295621; MARPAT 146:295621
 AB The present invention relates to a process for preparing
 N-ethyl-N-methyl-3-[(1S)-1-(dimethylamino)ethyl]phenyl carbamate
 (rivastigmine) and its tartrate, which comprises reacting
 3-[(1S)-1-(dimethylamino)ethyl]phenol or salts with phosgene, diphosgene
 or triphosgene, followed by the addition of N-methylethanamine to give
 rivastigmine. The tartrate was obtained by reacting rivastigmine with
 L-(+)-tartaric acid. The process has the advantages of high
 yield and optical purity.
 IT 123441-03-2P, Rivastigmine
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
 (Reactant or reagent)
 (preparation of rivastigmine and tartrate)
 RN 123441-03-2 CAPLUS
 CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl
 ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



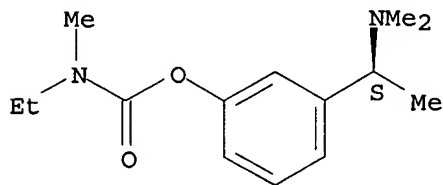
IT 129101-54-8P, Rivastigmine tartrate
 RL: SPN (Synthetic preparation); PREP (Preparation)
 (preparation of rivastigmine and tartrate)
 RN 129101-54-8 CAPLUS
 CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl
 ester, (2R,3R)-2,3-dihydroxybutanedioate (1:1) (CA INDEX NAME)

CM 1

CRN 123441-03-2

CMF C14 H22 N2 O2

Absolute stereochemistry. Rotation (-).

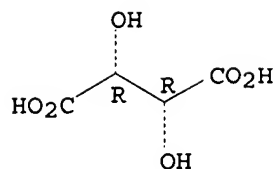


CM 2

CRN 87-69-4

CMF C4 H6 O6

Absolute stereochemistry.

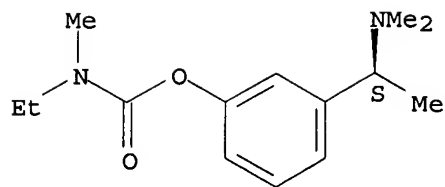


RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 9 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2007:257389 CAPLUS
DN 146:295628
TI Process for preparing enantiomerically pure rivastigmine
IN Jaweed, Mukarram Siddiqui Mohammed; Upadhye, Bhargav Krishnaji; Rai, Vikas Chandra; Zia, Hanfi
PA Wockhardt Limited, India
SO PCT Int. Appl., 16pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2007026373	A2	20070308	WO 2005-IN293	20050901
WO 2007026373	A3	20070712		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA				
PRAI WO 2005-IN293		20050901		
OS CASREACT 146:295628; MARPAT 146:295628				
AB An improved process for the preparation of enantiomerically pure rivastigmine, a selective acetylcholinesterase inhibitor, and its pharmaceutically acceptable salts is disclosed. Thus, 3-hydroxyacetophenone was treated with dimethylamine hydrochloride in presence of sodium cyanoborohydride to give an aminophenol. The aminophenol obtained was then treated with ethylmethylcarbamoyl chloride in presence of potassium tert-butoxide to obtain a carbamate. The carbamate was reacted di-p-toluoyl-D-tartaric acid in methanol to give a solid salt, which was recrystd. from methanol and basified with ammonia to give rivastigmine having > 99% enantiomeric purity.				
IT 123441-03-2P, Rivastigmine 129101-54-8P				
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)				
(preparation of enantiomerically pure rivastigmine and its salt from hydroxyacetophenone and carbamoyl halide)				
RN 123441-03-2 CAPLUS				
CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester (CA INDEX NAME)				

Absolute stereochemistry. Rotation (-).



RN 129101-54-8 CAPLUS

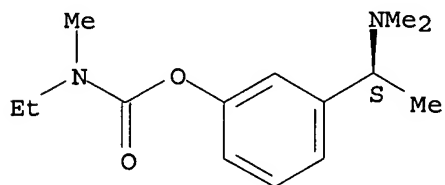
CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester, (2R,3R)-2,3-dihydroxybutanedioate (1:1) (CA INDEX NAME)

CM 1

CRN 123441-03-2

CMF C14 H22 N2 O2

Absolute stereochemistry. Rotation (-).

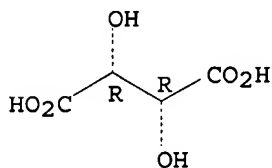


CM 2

CRN 87-69-4

CMF C4 H6 O6

Absolute stereochemistry.



IT 415973-05-6P, (R)-Rivastigmine

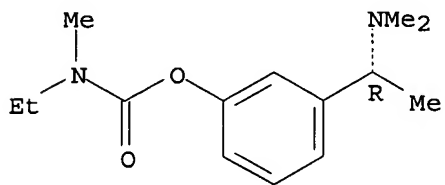
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of enantiomerically pure rivastigmine and its salt from hydroxyacetophenone and carbamoyl halide)

RN 415973-05-6 CAPLUS

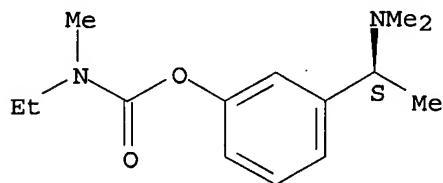
CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1R)-1-(dimethylamino)ethyl]phenyl ester (CA INDEX NAME)

Absolute stereochemistry. .



L10 ANSWER 10 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN
 AN 2007:225637 CAPLUS
 DN 146:477753
 TI Characterization of reversible and pseudo-irreversible
 acetylcholinesterase inhibitors by means of an immobilized enzyme reactor
 AU Bartolini, Manuela; Cavrini, Vanni; Andrisano, Vincenza
 CS Department of Pharmaceutical Sciences, University of Bologna, Bologna,
 40126, Italy
 SO Journal of Chromatography, A (2007), 1144(1), 102-110
 CODEN: JCRAEY; ISSN: 0021-9673
 PB Elsevier B.V.
 DT Journal
 LA English
 AB The aim of the present study was the application of a human AChE-CIM-IMER
 (enzyme reactor containing acetylcholinesterase immobilized on a monolithic
 disk) for the rapid evaluation of the thermodyn. and kinetic consts., and
 the mechanism of action of new selected inhibitors. For this application,
 human recombinant AChE was covalently immobilized onto an ethylenediamine
 (EDA) monolithic Convective Interaction Media (CIM) disk and online
 studies were performed by inserting this IMER into a HPLC system. Short
 anal. time, absence of backpressure, low nonspecific matrix interactions
 and immediate recovery of enzyme activity were the best characteristics of
 this AChE-CIM-IMER. Mechanisms of action of selected reversible
 inhibitors (tacrine, donepezil, edrophonium, ambenonium) were evaluated by
 means of Lineweaver-Burk plot anal. Analyses were performed online by
 injecting increasing concns. of the tested inhibitor and substrate and by
 monitoring the product peak area. AChE-CIM-IMER kinetic parameters (K_{app}
 and v_{appmax}) were derived as well as inhibitory consts. (K_{appi}) of
 selected compds. Moreover, noteworthy results were obtained in the
 application of the AChE-CIM-IMER to the characterization of the
 carbamylation and decarbamylation steps in pseudo-irreversible binding
 of carbamate derivs. (physostigmine and rivastigmine). AChE-CIM-IMER
 appeared to be a valid tool to determine simultaneously the kinetic consts. in
 a reliable and fast mode. The obtained values were found in agreement
 with those obtained with the classical methods with the free enzyme.
 Furthermore, after inactivation by carbamates, activity could be fully
 recovered and the AChE-CIM-IMER could be reused for further studies.
 Results showed that the AChE-CIM-IMER is a valid tool not only for
 automated fast screening in the first phase of the drug discovery
 process but also for the finest characterization of the mode of
 action of new hit compds. with increased accuracy and reproducibility and
 with saving of time and materials.
 IT 123441-03-2, Rivastigmine
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (characterization of reversible and pseudo-irreversible
 acetylcholinesterase inhibitors by means of immobilized enzyme reactor)
 RN 123441-03-2 CAPLUS
 CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl
 ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RE.CNT 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 11 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN

AN 2006:1210398 CAPLUS

DN 146:155046

TI Rivastigmine in Parkinson's disease dementia

AU Siddiqui, M. Asif A.; Wagstaff, Antona J.

CS Adis International Limited, Auckland, N. Z.

SO CNS Drugs (2006), 20(9), 739-747

CODEN: CNDREF; ISSN: 1172-7047

PB Adis International Ltd.

DT Journal; General Review

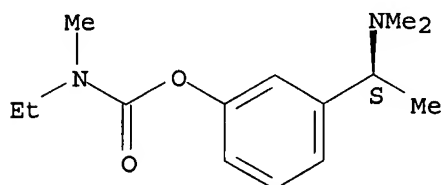
LA English

AB A review. Rivastigmine is a carbamate-type dual inhibitor of brain acetyl- and butyrylcholinesterases that has been evaluated in the symptomatic treatment of patients with mild to moderate dementia associated with idiopathic Parkinson's disease. Oral rivastigmine 3-12 mg/day for 24 wk was significantly more effective than placebo in ameliorating cognitive and functional decline, including attentional deficits, in patients with Parkinson's disease dementia in a randomized, double-blind trial. The beneficial effects of rivastigmine observed in the double-blind trial were generally maintained in a 24-wk extension of this study in which all patients received active treatment; placebo recipients who switched to rivastigmine also experienced improvements in their cognitive and functional symptoms at week 48. Rivastigmine appeared to be generally well tolerated, with the most common adverse events being mild to moderate in intensity and cholinergic in nature. Parkinsonian symptoms (mainly tremor) were more common in rivastigmine than placebo recipients. The hallmark of Parkinson's disease, the second most common neurodegenerative disorder, is motor system impairment causing resting tremor, bradykinesia, rigidity and postural instability. However, a combination of cognitive and neuropsychiatric symptoms is frequently found in these patients, and a progressive dementia syndrome develops in patients with longstanding disease, especially in elderly patients with severe disease. Dementia worsens the health-related quality of life of patients; it is associated with more rapid motor and functional decline, increased risk for institutionalization and increased mortality, as well as adding to caregiver distress. Patients with Parkinson's disease have an up to six-times higher risk of developing dementia than that in nondemented elderly patients without the disease. Approx. 28-44% of patients with Parkinson's disease experience dementia, with a cumulative prevalence of 78% reported over an 8-yr period in a longitudinal study using DSM-III revised diagnostic criteria. The presence of visual hallucinations or akinetic-dominant or mixed tremor/akinetic Parkinson's disease increases the risk of dementia 3-fold. The neuropathol. of Parkinson's disease dementia is likely a multifactorial process involving derangement of multiple populations of neurons in both the subcortical and cortical regions. A greater cholinergic deficit has been reported in Parkinson's disease dementia than in Alzheimer's disease; the extent of this deficit correlates with the severity of cognitive symptoms. Of the two cholinesterases hydrolyzing acetylcholine in the human brain, acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE), initial research has focused on the inhibition of AChE as cholinergic therapy of dementias. However, there is an increasing recognition of the role of BuChE in the normal and diseased brain. Current evidence indicates that, as AChE activity declines with the progressive loss of cortical neurons in Alzheimer's disease, BuChE levels increase and may take over the function to metabolize acetylcholine at the synapse. Furthermore, in dementia of Lewy bodies, the rate of cognitive decline has been shown to correlate with BuChE levels in the temporal cortex. Therefore, there may be at least a theor. advantage of a dual inhibitor of AChE and BuChE over a selective AChE inhibitor. Rivastigmine is a carbamate-type, dual inhibitor of AChE and BuChE that has been widely used as a cholinergic agent in the symptomatic treatment of Alzheimer's disease; the efficacy and tolerability of rivastigmine in this indication have been reviewed previously. This article focuses on the use of rivastigmine in dementia

associated with Parkinson's disease.

IT 123441-03-2, Rivastigmine
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)
(use of rivastigmine in treatment of patients with dementia associated
with Parkinson's disease)
RN 123441-03-2 CAPLUS
CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl
ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



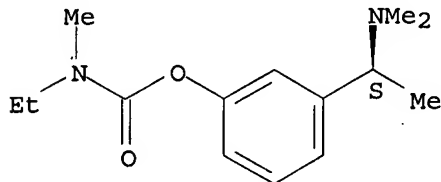
RE.CNT 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 12 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2006:533544 CAPLUS
DN 145:465467
TI Are cholinergic enhancers beneficial for memory in schizophrenia? An
event-related potentials (ERPs) study of rivastigmine add-on therapy in a
crossover trial
AU Guillem, Francois; Chouinard, Sylvie; Poulin, Julie; Godbout, Roger;
Lalonde, Pierre; Melun, Pierre; Bentaleb, Lahcen Ait; Stip, Emmanuel
CS Hopital L-H Lafontaine, Centre de Recherche Fernand-Seguin, Montreal, QC,
H1N 3V2, Can.
SO Progress in Neuro-Psychopharmacology & Biological Psychiatry (2006),
30(5), 934-945
CODEN: PNPPD7; ISSN: 0278-5846
PB Elsevier B.V.
DT Journal
LA English
AB Studies have reported beneficial effects of cholinergic enhancers, e.g.,
rivastigmine, on memory in schizophrenia but others have not. Possibly,
these discrepancies are related to the lack of specificity of the tests
used. This study investigated the effect of rivastigmine on memory in
schizophrenia using event-related potentials (ERPs). Eighteen patients
treated with atypical antipsychotic received rivastigmine adjuvant therapy
in a randomized, crossover design. They were assessed at baseline (T1)
and on two subsequent occasions (T2 and T3), where one half of the
subjects were taken rivastigmine and the other half not. ERPs were
recorded during a recognition memory task on each session. Behavioral and
ERP data were analyzed using mixed ANOVA models first at T1 to detect
potential group differences and for the trial (T1-T2) to determine the
influence of rivastigmine, i.e., session+group interactions. The
results showed no group difference at T1 except a trend for one group to
be less efficient than the other on RT measures. When controlling for
this difference the results on the trial data showed a trend for a benefit
of rivastigmine on the RT memory effect. ERP anal. revealed that
rivastigmine affects the amplitudes of two components elicited within
150-300 ms over posterior (reduced N2b) and frontal sites (enhanced P2a).
It also enhances the magnitude of the memory (old/new) effect on two later
components over posterior (N400) and frontal sites (F-N400). These
results suggest that rivastigmine improves selective attention by
enhancing interference inhibition processes (P2a) and lowering
the reactivity to incoming stimulus (N2b). It also improves the
integration of information with knowledge (N400) and with its context

(F-N400). Generally, this study showed that the beneficial effect of rivastigmine on memory is not unitary but rather comes from its action at different time points within information processing cascade.

IT 123441-03-2, Rivastigmine
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(acetylcholinesterase inhibitor rivastigmine adjuvant therapy improved memory in schizophrenic patient)
RN 123441-03-2 CAPLUS
CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RE.CNT 90 THERE ARE 90 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 13 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN

AN 2006:155049 CAPLUS

DN 145:76443

TI Short-term treatment with rivastigmine and plasma levels of A β peptides in Alzheimer's disease

AU Sobow, Tomasz; Kloszewska, Iwona

CS Department of Old Age Psychiatry and Psychotic Disorders, Medical University of Lodz, Lodz, 92-216, Pol.

SO Folia Neuropathologica (2005), 43(4), 340-344

CODEN: FONEEW; ISSN: 1641-4640

PB Termedia Publishing House

DT Journal

LA English

AB Deregulation of APP metabolism is considered to be a key pathogenic event in Alzheimer's disease. Data from cell cultures indicate that the secretion of A β 1-42 might be inhibited by cholinesterase inhibitors, possibly via M1 receptors stimulation. Treatment with tacrine, a dual acetyl- and butyrylcholinesterase inhibitor, had no significant effect on mean plasma A β species concns. However, a correlation was observed between higher drug concns. and lower A β levels that might indicate an effect on APP metabolism with an increased α -cleavage. A β 1-40 and A β 1-42 levels were measured in the plasma of 28 AD subjects by means of a com. available ELISA before rivastigmine treatment and at week 2 after the first dose of the drug (3 mg/day) had been administered. Treatment with rivastigmine exhibited a significant effect on mean plasma concns. of A β 1-42 (mean difference 7.8 ± 8.4 , $t = -4.9$, $p_{\text{mean difference}} 7.8 \pm 8.4$, $t = -4.9$, $p < 0.001$) with a neg. correlation with the patients age (Pearson's $R = -0.40$, $p = 0.035$). No significant effect on plasma A β 1-40 was observed. The observed increase of mean levels of plasma A β 1-42 after rivastigmine treatment might indicate an effect of the drug on A β metabolism, mobilization of A β 1-42 from deposits in the affected brain areas and a consecutive A β 1-42 brain-to-plasma efflux. The neg. correlation between A β 1-42 plasma levels changes and age may be a sign of impairment of this process in the older patients. A large individual variation of the observed response, however, excludes drawing definite conclusions. Whether those subjects who respond to rivastigmine in terms of A β 1-42 plasma levels changes also respond clin. needs to be established.

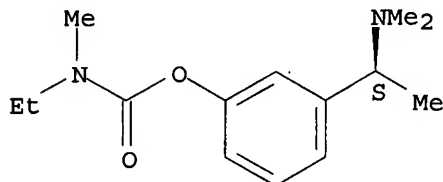
IT 123441-03-2, Rivastigmine

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)
(short-term rivastigmine did not affect A β 1-40, but significantly
increased plasma A β 1-42 level and decreased A β 1-40/A β 1-
42 ratio which was correlated with age in Alzheimer's disease patient)

RN 123441-03-2 CAPLUS

CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl
ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RE.CNT 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 14 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN

AN 2005:1137923 CAPLUS

DN 143:399619

TI Rivastigmine is a potent inhibitor of acetyl- and butyrylcholinesterase in
Alzheimer's plaques and tangles

AU Eskander, Mariam F.; Nagykerly, Nicholas G.; Leung, Elaine Y.; Khelghati,
Bahiyiyih; Geula, Changiz

CS Laboratory for Neurodegenerative and Aging Research, Department of
Medicine (Neuroscience), Harvard Medical School and Division of
Gerontology, Beth Israel Deaconess Medical Center, Boston, MA, 02215, USA

SO Brain Research (2005), 1060(1-2), 144-152

CODEN: BRREAP; ISSN: 0006-8993

PB Elsevier B.V.

DT Journal

LA English

AB Acetylcholinesterase and butyrylcholinesterase activities emerge in
association with plaques and tangles in Alzheimer's disease. These pathol.
cholinesterases, with altered properties, are suggested to participate in
formation of plaques. The present experiment assessed the ability of
rivastigmine, a clin. utilized agent that inhibits acetylcholinesterase
and butyrylcholinesterase activities, to inhibit cholinesterases in
plaques and tangles. Cortical sections from cases of Alzheimer's disease
were processed using cholinesterase histochem. in the presence or absence
of rivastigmine. Optical densities of stained sections were utilized as a
measure of inhibition. The potency of rivastigmine was compared with
those of other specific inhibitors. Optimum staining for cholinesterases
in neurons and axons was obtained at pH 8.0. Cholinesterases in plaques,
tangles and glia were stained best at pH 6.8. Butyrylcholinesterase-pos.
plaques were more numerous than acetylcholinesterase-pos. plaques.
Rivastigmine inhibited acetylcholinesterase in all pos. structures in a
dose-dependent manner (10⁻⁶-10⁻⁴ M). However, even at the highest
concentration,

faint activity remained. In contrast, rivastigmine resulted in complete
inhibition of butyrylcholinesterase in all structures at 10⁻⁵ M.
Rivastigmine was equipotent to the specific acetylcholinesterase inhibitor
BW284C51 and more potent than the butyrylcholinesterase inhibitors
iso-OMPA and ethopropazine. In conclusion, rivastigmine is a potent
inhibitor of acetylcholinesterase and a more potent inhibitor of
butyrylcholinesterase in plaques and tangles. Unlike other cholinesterase
inhibitors tested, rivastigmine inhibited cholinesterases in normal and
pathol. structures with the same potency. Thus, at the therapeutic
concns. used, rivastigmine is likely to result in inhibition of pathol.

cholinesterases, with the potential of interfering with the disease process.

IT 123441-03-2, Rivastigmine

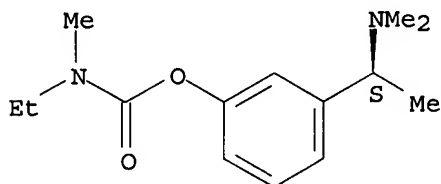
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(rivastigmine is a potent inhibitor of acetyl- and butyrylcholinesterase in Alzheimer's plaques and tangles)

RN 123441-03-2 CAPLUS

CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RE.CNT 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 15 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN

AN 2005:1135771 CAPLUS

DN 143:416054

TI Modulation of memory and visuospatial processes by biperiden and rivastigmine in elderly healthy subjects

AU Wezenberg, E.; Verkes, R. J.; Sabbe, B. G. C.; Ruigt, G. S. F.; Hulstijn, W.

CS Department of Psychiatry (333), Radboud University Nijmegen Medical Center, Nijmegen, 6500, Neth.

SO Psychopharmacology (Berlin, Germany) (2005), 181(3), 582-594
CODEN: PSCHDL; ISSN: 0033-3158

PB Springer GmbH

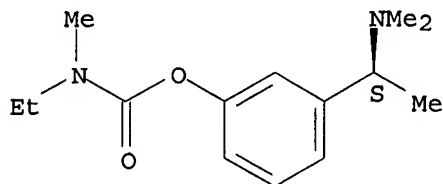
DT Journal

LA English

AB The central cholinergic system is implicated in cognitive functioning. The dysfunction of this system is expressed in many diseases like Alzheimer's disease, dementia of Lewy body, Parkinson's disease and vascular dementia. In recent animal studies, it was found that selective cholinergic modulation affects visuospatial processes even more than memory function. In the current study, the authors tried to replicate those findings. In order to investigate the acute effects of cholinergic drugs on memory and visuospatial functions, a selective anticholinergic drug, biperiden, was compared to a selective acetylcholinesterase-inhibiting drug, rivastigmine, in healthy elderly subjects. A double-blind, placebo-controlled, randomized, cross-over study was performed in 16 healthy, elderly volunteers (eight men, eight women; mean age 66.1, SD 4.46 years). All subjects received biperiden (2 mg), rivastigmine (3 mg) and placebo with an interval of 7 days between them. Testing took place 1 h after drug intake (which was around T_{max} for both drugs). Subjects were presented with tests for episodic memory (word list and picture memory), working memory tasks (N-back, symbol recall) and motor learning (maze task, pursuit rotor). Visuospatial abilities were assessed by tests with high visual scanning components (tangled lines and Symbol Digit Substitution Test). Episodic memory was impaired by biperiden. Rivastigmine impaired recognition parts of the episodic memory performance. Working memory was nonsignificantly impaired by biperiden and not affected by rivastigmine. Motor learning as well as visuospatial processes were impaired by biperiden and improved by rivastigmine. These results implicate acetylcholine as a modulator not only of memory but also of visuospatial abilities.

IT 123441-03-2, Rivastigmine
 RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (modulation of memory and visuospatial processes by biperiden and rivastigmine in elderly healthy subjects)
 RN 123441-03-2 CAPLUS
 CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RE.CNT 79 THERE ARE 79 CITED REFERENCES AVAILABLE FOR THIS RECORD
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 16 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN
 AN 2005:1132655 CAPLUS
 DN 143:393091
 TI System and a method for producing layered oral dosage forms
 IN Figueroa, Iddys D.; Ruiz, Orlando
 PA USA
 SO U.S. Pat. Appl. Publ., 17 pp.
 CODEN: USXXCO
 DT Patent
 LA English
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2005233000	A1	20051020	US 2004-825870	20040416
	WO 2005105038	A2	20051110	WO 2005-US11941	20050408
	WO 2005105038	A3	20070329		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP	1758551	A2	20070307	EP 2005-734352	20050408
	R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, LV, MK, YU				

PRAI US 2004-825870 A 20040416
 WO 2005-US11941 W 20050408

AB A method for producing an oral medication includes dispensing a structural material, the structural material including one of a polymer or a gelatin, curing the structural material, and dispensing a jettable pharmaceutical solution onto the cured structural material.

IT 129101-54-8, Rivastigmine tartrate
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses) (producing layered oral dosage forms)

RN 129101-54-8 CAPLUS

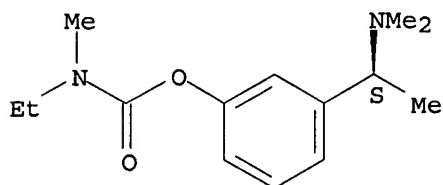
CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester, (2R,3R)-2,3-dihydroxybutanedioate (1:1) (CA INDEX NAME)

CM 1

CRN 123441-03-2

CMF C14 H22 N2 O2

Absolute stereochemistry. Rotation (-).

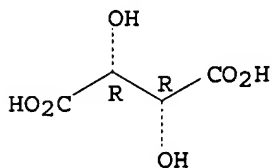


CM 2

CRN 87-69-4

CMF C4 H6 O6

Absolute stereochemistry.



L10. ANSWER 17 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN

AN 2005:1021603 CAPLUS

DN 143:311990

TI Combined pharmaceutical composition for the inhibition of the decline of cognitive functions

IN Levay, Gyoergy; Gacsalyi, Istvan; Harsing, Laszlo Gabor; Simig, Gyula

PA Egis Gyogyszergyar Rt., Hung.

SO PCT Int. Appl., 24 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2005087212	A1	20050922	WO 2004-HU22	20040312
	W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
	RW:	BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
	AU 2004317129	A1	20050922	AU 2004-317129	20040312
	CA 2559493	A1	20050922	CA 2004-2559493	20040312
	EP 1727531	A1	20061206	EP 2004-720092	20040312

R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LI, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL, LT, LV, MK

CN 1925849	A	20070307	CN 2004-80042405	20040312
BR 2004018634	A	20070529	BR 2004-18634	20040312
JP 2007528892	T	20071018	JP 2007-502417	20040312
IN 2006DN05448	A	20070803	IN 2006-DN5448	20060919
NO 2006004644	A	20061211	NO 2006-4644	20061012
BG 109701	A	20070630	BG 2006-109701	20061012
PRAI WO 2004-HU22	A	20040312		

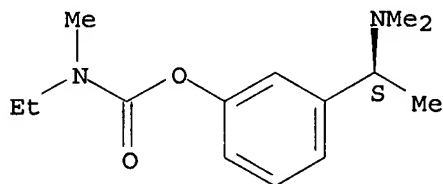
AB The invention relates to a combined pharmaceutical composition for the inhibition of the decline of cognitive functions comprising as A) component (1R,2S,4R)-(-)-2-[N,N-(dimethylaminoethoxy)]-2-phenyl-1,7,7-trimethylbicyclo]-2-phenyl-1.7.-trimethylbicyclo[2.2.1]heptane of the formula (I) or a pharmaceutically acceptable acid addition salt thereof and as B) component a nootropic, an inhibitor of the acetylcholinesterase enzyme and/or a further pharmaceutical active ingredient which exhibits a beneficial effect on the cognitive processes in admixt. with suitable inert pharmaceutical carriers and/or auxiliary agents. The combined pharmaceutical composition according to the present invention can be particularly used for the treatment of Alzheimer disease or other diseases showing similar symptoms, diseases accompanied by malfunctions of intellectual abilities (e.g. mental decline in schizophrenia), mental decline in elderly (dementias in elderly), Korsakoff syndrome, Huntington syndrome, Parkinson syndrome or mental decline produced by alcoholism.

IT 123441-03-2, Rivastigmine
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (combined pharmaceutical composition for inhibition of decline of cognitive functions)

RN 123441-03-2 CAPLUS

CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RE.CNT 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 18 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN
 AN 2005:983611 CAPLUS
 DN 143:292527
 TI Bioavailability and improved delivery of alkaline pharmaceutical drugs
 IN Yu, Ruey J.; Van Scott, Eugene J.
 PA USA
 SO U.S. Pat. Appl. Publ., 16 pp., Cont.-in-part of U.S. Ser. No. 792,273.
 CODEN: USXXCO
 DT Patent
 LA English

FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	-----	---	-----	-----	-----
PI	US 2005196418	A1	20050908	US 2005-50434	20050204
	US 2004214215	A1	20041028	US 2004-792273	20040304
	WO 2006084174	A2	20060810	WO 2006-US3917	20060206
	WO 2006084174	A3	20071004		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,

CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA

PRAI US 2004-792273 A2 20040304
US 2003-452557P P 20030307
US 2005-50434 A 20050204

OS MARPAT 143:292527

AB Embodiments of the invention relate to a composition, a process of making the composition, and to the use of the composition The compns. include a

mol. complex formed between an alkaline pharmaceutical drug and at least one selected from a hydroxy acid, a polyhydroxy acid, a related acid, a lactone, or combinations thereof. The compns. provide improved bioavailability and improved delivery of the drug into the cutaneous tissues. For example, diphenhydramine hydrochloride 29 g (0.1 mol) was dissolved in water and 5 N sodium hydroxide generating diphenhydramine free base. Gluconolactone 18 g (0.1 mol) was added to form a mol. complex of 0.1 mol diphenhydramine free base with 0.1 mol gluconic acid/gluconolactone. The solution thus obtained was used for various forms of topical formulations including oil-in-water creams, lotions, gels and solns.

IT 123441-03-2, Rivastigmine

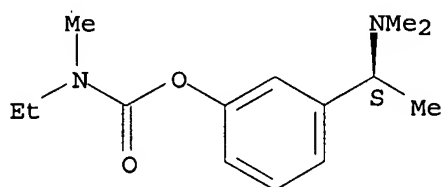
RL: RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)

(bioavailability and improved delivery of alkaline drugs by complexation with acids or lactones)

RN 123441-03-2 CAPLUS

CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L10 ANSWER 19 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN

AN 2005:602193 CAPLUS

DN 143:399502

TI Effects of Rivastigmine on Sustained Attention in Schizophrenia: An fMRI Study

AU Aasen, Ingrid; Kumari, Veena; Sharma, Tonmoy

CS Department of Psychology, Institute of Psychiatry, London, UK

SO Journal of Clinical Psychopharmacology (2005), 25(4), 311-317

CODEN: JCPYDR; ISSN: 0271-0749

PB Lippincott Williams & Wilkins

DT Journal

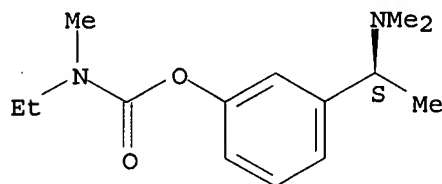
LA English

AB This study assessed the neural correlates of the effects of rivastigmine, a CNS-selective cholinesterase inhibitor, given as an add-on therapy to antipsychotics-treated patients with schizophrenia who displayed moderate

cognitive impairments, using functional magnetic resonance imaging (fMRI) during a sustained attention task. The study used a placebo-controlled, randomized, double-blind longitudinal design. Twenty patients stable on antipsychotics, 11 assigned to receive rivastigmine and 9 to receive placebo, underwent fMRI and clin. assessments at baseline and after 12 wk. The fMRI task used a periodic block design and involved 3 conditions: rest, detecting a nonzero number ("nonzero" condition), and detecting a specific number ("specific number" condition) among a series of 6-digit nos. Online data (via button presses) were acquired on both occasions. Behavioral results showed a trend (P = 0.075) for the rivastigmine-treated patients to have more correct responses and the placebo group to have fewer correct responses at 12 wk compared with baseline in the "nonzero" condition. There was also an increase in regional brain activity in the cerebellum in the rivastigmine group at 12 wk in both conditions, which was only partially explained by change in behavioral measures; no change was observed in the placebo group. Our results showed that rivastigmine treatment increased cerebellar activity and influenced attentional processes.

IT 123441-03-2, Rivastigmine
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (rivastigmine treatment increased cerebellar activity and improved attention process in patient with schizophrenia)
 RN 123441-03-2 CAPLUS
 CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



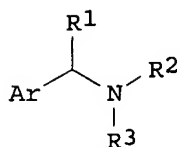
RE.CNT 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 20 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN
 AN 2005:564631 CAPLUS
 DN 143:97092
 TI Stereoselective process for the preparation of tertiary amines attached to a secondary carbon center using a chiral transition metal transfer hydrogenation catalyst
 IN Fieldhouse, Robin
 PA Avecia Pharmaceuticals Limited, UK
 SO PCT Int. Appl., 32 pp.
 CODEN: PIXXD2
 DT Patent
 LA English
 FAN.CNT 1

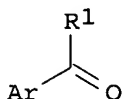
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005058804	A1	20050630	WO 2004-GB5199	20041208
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,				

EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT,
RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML,
MR, NE, SN, TD, TG.

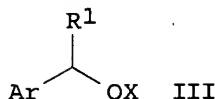
PRAI GB 2003-29284 A 20031218
OS CASREACT 143:97092; MARPAT 143:97092
GI



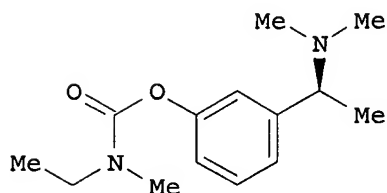
I



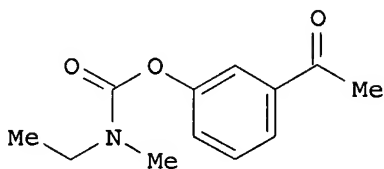
II



III



IV



V

AB The invention provides a process for preparing tertiary amines I in three steps. In compds. I, Ar is (un)substituted hydrocarbon or (un)substituted heterocyclyl group comprising an aromatic moiety; and R1, R2, and R3 are independently selected from (un)substituted hydrocarbon and (un)substituted heterocyclyl. Ketone II is reduced to the corresponding secondary alc. by transfer hydrogenation. The alc. is converted to a leaving group to form compound III using the corresponding anhydride X-O-X (X = acetyl, trifluoroacetyl, methanesulfonyl, trifluoromethanesulfonyl, 4-toluenesulfonyl). Substitution of the leaving group with an amine (R2R3NH) then yields tertiary amine I. The invention also provides a stereoselective process for the preparation of I, where Ar and R1 are different. In this way, rivastigmine (IV) was prepared in 83% yield (3 steps) by way of an asym. transfer hydrogenation of V using a chiral rhodium catalyst. The preferred catalysts can be prepared in situ from bis[dichloro(pentamethylcyclopentadienyl)rhodium] and chiral N-camphorsulfonyl-1,2-diphenylethylene-1,2-diamine.

IT 123441-03-2P, Rivastigmine

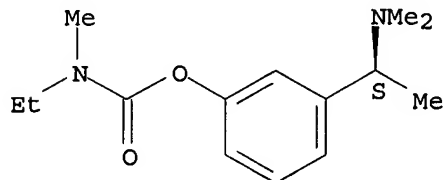
RL: SPN (Synthetic preparation); PREP (Preparation)

(process for the stereoselective preparation of tertiary amines attached to a secondary carbon center)

RN 123441-03-2 CAPLUS

CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 21 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN

AN 2005:561746 CAPLUS

DN 143:77963

TI Process for the preparation of aminoalkylphenyl carbamates in particular rivastigmine hydrogentartrate

IN Gaitonde, Abhay; Mangle, Mangesh

PA Generics UK Limited, UK

SO Brit. UK Pat. Appl., 13 pp.

CODEN: BAXXDU

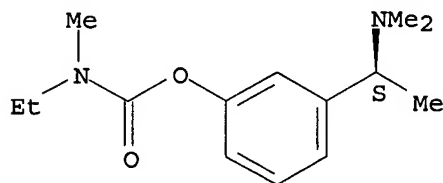
DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	GB 2409453	A	20050629	GB 2003-29970	20031224
	WO 2005061446	A2	20050707	WO 2004-GB50042	20041217
	WO 2005061446	A3	20060105		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, SM				
	RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	EP 1697313	A2	20060906	EP 2004-806260	20041217
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK, IS				
PRAI	GB 2003-29970	A	20031224		
	WO 2004-GB50042	W	20041217		
OS	CASREACT 143:77963; MARPAT 143:77963				
AB	Rivastigmine hydrogentartrate is prepared from 3-hydroxyacetophenone in a process which has the advantage of avoiding the preparation of zwitterionic intermediates which are very water soluble and need to be isolated by concentration of aqueous solvent; this process is therefore suited to the industrial-scale manufacture of aminoalkylphenyl carbamates. The large amts. of sulfated ash residues left in the product when prepared by prior-art processes and the use of pyrophoric and reagents such as sodium hydride may be avoided by using the title method.				
IT	123441-03-2P, Rivastigmine 129101-54-8P, Rivastigmine hydrogentartrate				
	RL: RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)				
	(process for the preparation of aminoalkylphenyl carbamates in particular rivastigmine hydrogentartrate)				
RN	123441-03-2 CAPLUS				
CN	Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester (CA INDEX NAME)				

Absolute stereochemistry. Rotation (-).



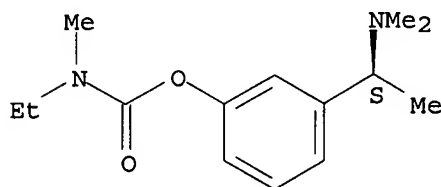
RN 129101-54-8 CAPLUS
CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester, (2R,3R)-2,3-dihydroxybutanedioate (1:1) (CA INDEX NAME)

CM 1

CRN 123441-03-2

CMF C14 H22 N2 O2

Absolute stereochemistry. Rotation (-).

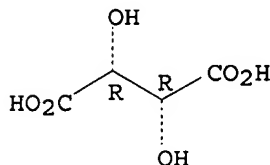


CM 2

CRN 87-69-4

CMF C4 H6 O6

Absolute stereochemistry.



RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 22 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN

AN 2004:1063811 CAPLUS

DN 142:373547

TI Process for preparation of 3-[(1S)-1-(dimethylamino)ethyl]phenyl N-ethyl-N-methylcarbamate and its salts

IN Zhou, Ning; Xu, Xingxiang; Zhou, Zhishan

PA Sanwei Pharmaceutical Co., Ltd., Shanghai, Peop. Rep. China

SO Faming Zhuanli Shenqing Gongkai Shuomingshu, 9 pp.

CODEN: CNXXEV

DT Patent

LA Chinese

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	CN 1486973	A	20040407	CN 2003-141995	20030731
PRAI	CN 2003-141995		20030731		

OS CASREACT 142:373547

AB This invention pertains to a method for producing 3-[(1S)-1-(Dimethylamino)ethyl]phenyl N-ethyl-N-methylcarbamate and its salts by esterifying (S)-3-(1-dimethylaminoethyl)phenol with N-ethyl-N-methylcarbamoyl chloride in organic solvent (such as toluene, xylene, chlorobenzene, Et ether, THF, etc.) in the presence of a base (such as NaH, NaOH, triethylamine, etc.) at (-20)-70 °C, and adding an acid in alc. (ether, or Et acetate) solvent. The synthetic N-ethyl-N-methylcarbamate salts may be used for treating senile dementia

(no data).

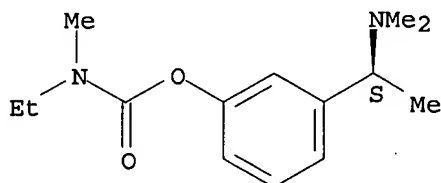
IT 123441-03-2P

RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of 3-[(1S)-1-(dimethylamino)ethyl]phenyl N-ethyl-N-methylcarbamate and its salts)

RN 123441-03-2 CAPLUS

CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



IT 129101-54-8P 727418-36-2P 849466-24-6P

849466-25-7P 849466-28-0P 849466-31-5P

RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(preparation of 3-[(1S)-1-(dimethylamino)ethyl]phenyl N-ethyl-N-methylcarbamate and its salts)

RN 129101-54-8 CAPLUS

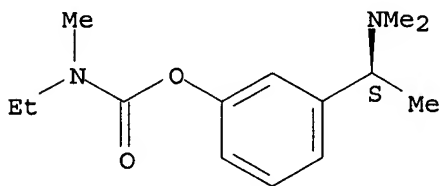
CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester, (2R,3R)-2,3-dihydroxybutanedioate (1:1) (CA INDEX NAME)

CM 1

CRN 123441-03-2

CMF C14 H22 N2 O2

Absolute stereochemistry. Rotation (-).

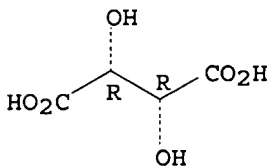


CM 2

CRN 87-69-4

CMF C4 H6 O6

Absolute stereochemistry.

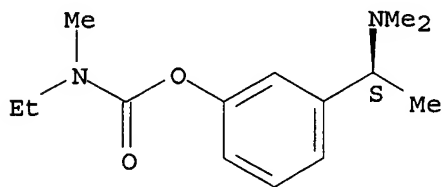


RN 727418-36-2 CAPLUS

CN Carbamic acid, ethylmethyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester,

monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



● HCl

RN 849466-24-6 CAPLUS

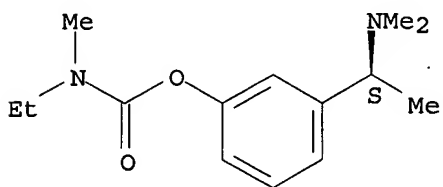
CN Carbamic acid, ethylmethyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester,
(2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 123441-03-2

CMF C14 H22 N2 O2

Absolute stereochemistry. Rotation (-).

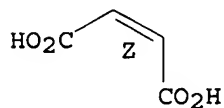


CM 2

CRN 110-16-7

CMF C4 H4 O4

Double bond geometry as shown.



RN 849466-25-7 CAPLUS

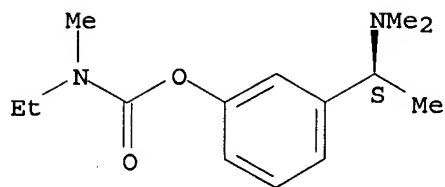
CN Carbamic acid, ethylmethyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester,
(2E)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 123441-03-2

CMF C14 H22 N2 O2

Absolute stereochemistry. Rotation (-).

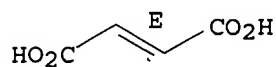


CM 2

CRN 110-17-8

CMF C4 H4 O4

Double bond geometry as shown.



RN 849466-28-0 CAPLUS

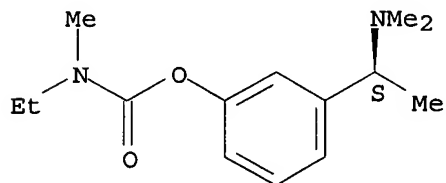
CN Carbamic acid, ethylmethyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester, 2-hydroxy-1,2,3-propanetricarboxylate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 123441-03-2

CMF C14 H22 N2 O2

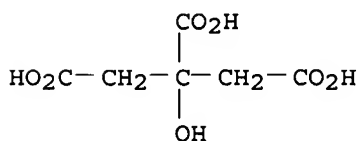
Absolute stereochemistry. Rotation (-).



CM 2

CRN 77-92-9

CMF C6 H8 O7



RN 849466-31-5 CAPLUS

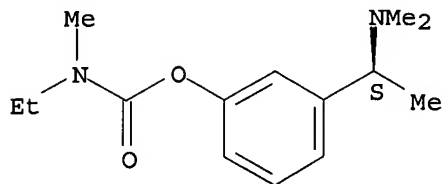
CN Carbamic acid, ethylmethyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester, sulfate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 123441-03-2

CMF C14 H22 N2 O2

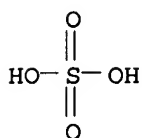
Absolute stereochemistry.. Rotation (-).



CM 2

CRN 7664-93-9

CMF H2 O4 S



L10 ANSWER 23 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN

AN 2004:622247 CAPLUS

DN 142:6315

TI Process for preparing (-)-(S)-3-[1-(dimethylamino)ethyl]phenyl
N-ethyl-N-methylcarbamate (rivastigmine)

IN Stepankova, Hana; Hajicek, Josef; Simek, Stanislav

PA Leciva, A. S., Czech Rep.

SO Czech Rep., 12 pp.

CODEN: CZXXED

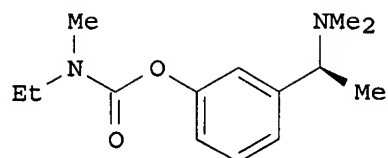
DT Patent

LA Czech

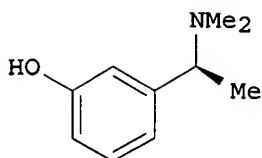
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	CZ 293014	B6	20040114	CZ 2002-3555	20021024
	WO 2004037771	A1	20040506	WO 2003-CZ58	20031021
	W:				
	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,				
	CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE,				
	GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK,				
	LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ,				
	OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM,				
	TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW:				
	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,				
	KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,				
	FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,				
	BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	AU 2003277795	A1	20040513	AU 2003-277795	20031021
	EP 1556338	A1	20050727	EP 2003-769173	20031021
	R:				
	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,				
	IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
	US 2006122417	A1	20060608	US 2005-523927	20050207
PRAI	CZ 2002-3555	A	20021024		
	WO 2003-CZ58	W	20031021		

GI



I



II

AB The invention relates to the process of preparing the title compound (S)-I or its tartrate salt which comprises (a) reacting (S)-II (preparation given starting from 3-methoxyacetophenone) with EtN(Me)COX [wherein X = a leaving group] to provide (S)-I, and (b) treating (S)-I with tartaric acid to afford (S)-I.tartrate.

IT 123441-03-2P, Rivastigmine 129101-54-8P, Rivastigmine tartrate

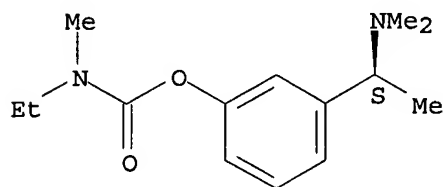
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(process for preparing (-)-(S)-3-[1-(dimethylamino)ethyl]phenyl N-ethyl-N-methylcarbamate (rivastigmine))

RN 123441-03-2 CAPLUS

CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 129101-54-8 CAPLUS

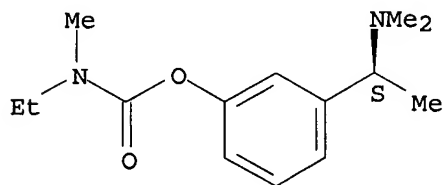
CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester, (2R,3R)-2,3-dihydroxybutanedioate (1:1) (CA INDEX NAME)

CM 1

CRN 123441-03-2

CMF C14 H22 N2 O2

Absolute stereochemistry. Rotation (-).

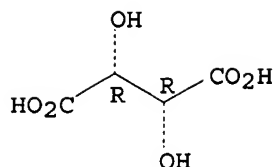


CM 2

CRN 87-69-4

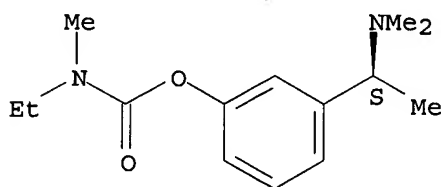
CMF C4 H6 O6

Absolute stereochemistry.



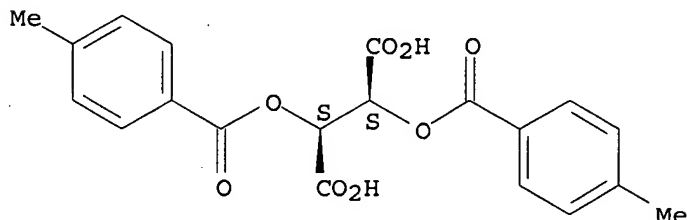
IT 399515-02-7P
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
 (Reactant or reagent)
 (process for preparing (-)-(S)-3-[1-(dimethylamino)ethyl]phenyl
 N-ethyl-N-methylcarbamate (rivastigmine))
 RN 399515-02-7 CAPLUS
 CN Butanedioic acid, 2,3-bis[(4-methylbenzoyl)oxy]-, (2S,3S)-, compd. with
 3-[(1S)-1-(dimethylamino)ethyl]phenyl ethylmethylcarbamate (1:1) (9CI)
 (CA INDEX NAME)
 CM 1
 CRN 123441-03-2
 CMF C14 H22 N2 O2

Absolute stereochemistry. Rotation (-).



CM 2
 CRN 32634-68-7
 CMF C20 H18 O8

Absolute stereochemistry. Rotation (+).



L10 ANSWER 24 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN
 AN 2004:476369 CAPLUS
 DN 141:405520
 TI Acetylcholinesterase and its inhibition in Alzheimer disease
 AU Lane, Roger M.; Kivipelto, Miia; Greig, Nigel H.
 CS Novartis Neuroscience, Novartis Pharmaceuticals Corp, Pfizer Inc., East
 Hanover, NJ, USA
 SO Clinical Neuropharmacology (2004), 27(3), 141-149
 CODEN: CLNEDB; ISSN: 0362-5664
 PB Lippincott Williams & Wilkins
 DT Journal; General Review
 LA English

AB A review. Until recently, the only established function of acetylcholinesterase (AChE) was the termination of cholinergic neurotransmission. Therefore, the use of AChE inhibitors to treat symptoms caused by cholinergic imbalances in Alzheimer disease (AD) represented a rational approach. However, it is now clear that AChE and the cholinergic system may have broader effects in AD. Of particular interest may be signal transduction pathways mediated through cholinergic receptors that promote nonamyloidogenic amyloid precursor protein processing and decrease tau phosphorylation, and the role of AChE in the aggregation of β -amyloid (A β) peptide. In addition, the neuronal and nonneuronal cholinergic systems have important roles in the modulation of regional cerebral blood flow. These findings may modify the overly simplistic cholinergic hypothesis in AD that is limited to symptomatic treatment and ignores the potential of cholinergic therapies as disease-modifying agents. Chronic increases in AChE activity may exacerbate neurodegenerative processes, make clin. relevant levels of AChE inhibition more difficult to achieve, and cause the therapeutic value of cholinesterase inhibitors (ChE-Is) to be limited and temporary. Rapidly reversible ChE-Is appear to increase AChE activity over the longer term whereas, remarkably, irreversible or very slowly reversible ChE-Is do not seem to have this effect. If such differences between ChE-Is are shown to have clin. correlates, this may prompt reconsideration of the rationale and expectations of some agents in the long-term management of AD.

IT 123441-03-2, Rivastigmine

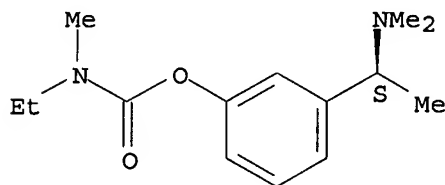
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(ChE-Is, donepezil, galantamine and tacrine induced marked elevations of AChE level showing adverse consequences in long term treatment but rivastigmine could not elevate AChE target enzyme level in brain of AD)

RN 123441-03-2 CAPLUS

CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RE.CNT 102 THERE ARE 102 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 25 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN

AN 2004:64842 CAPLUS

DN 140:86958

TI Acetylcholinesterase inhibition in Alzheimer's disease

AU Ibach, Bernd; Haen, Ekkehard

CS Memory Disorders Clinic, Gerontopsychiatric and Clinical Pharmacology Research Unit, Department of Psychiatry, University of Regensburg, Regensburg, Germany

SO Current Pharmaceutical Design (2004), 10(3), 231-251

CODEN: CPDEFP; ISSN: 1381-6128

PB Bentham Science Publishers Ltd.

DT Journal; General Review

LA English

AB A review. Alzheimer's disease (AD) is the most common cause for dementia in our aging population, which leads to a slowly progressive, irretrievable ruination of mental function. The destructive, primarily degenerative condition is neuropathol. characterized by the formation of

amyloid plaques, neurofibrillary tangles and loss of neurons and synapses as well. Research during the past twenty years revealed early in the disease course a degeneration of cholinergic nuclei localized in the basal forebrain. Impairment of this cholinergic system, which projects into large areas of the limbic system and the neocortex is followed by disturbance of attentional processes and cognitive decline. The link between the cholinergic dysfunction and cognitive impairment has focused large scientific efforts to understand the neurobiol. of cognition and to develop therapeutic tools for the fight against Alzheimer's disease. Acetylcholinesterase inhibitors are currently the best established treatment for this devastating disease. This review describes historical aspects and the vast range of use of cholinesterase inhibitors in traditional societies and industrial nations. Second, the rational basis will be outlined for their development as medication, the so-called cholinergic hypotheses of AD. Third, acetylcholinesterase inhibitors currently available for the treatment of AD will be reviewed. This includes donepezil, galanthamine and rivastigmine. Tacrine, the first acetylcholinesterase inhibitor who became available in 1993 as a treatment for AD, does not play an essential role anymore besides his historical value, because of its hepatotoxicity. Although acetylcholinesterase inhibitors are no cure, these drugs can delay the progress of mental deterioration, reduce neuropsychiatric symptoms and therefore represent a rational therapeutic approach to the treatment of Alzheimer's Disease.

IT 123441-03-2, Rivastigmine

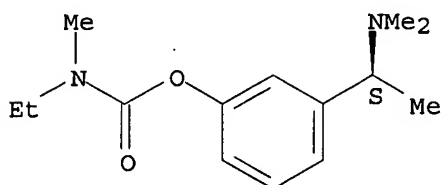
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(acetylcholinesterase inhibitors for treatment of Alzheimer's disease)

RN 123441-03-2 CAPLUS

CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RE.CNT 135 THERE ARE 135 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 26 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN

AN 2003:972013 CAPLUS

DN 140:27668

TI A process for the preparation of phenyl carbamates

IN Thennati, Rajamannar

PA Sun Pharmaceutical Industries Limited, India; Patel, Hetalkumar
Virendrabhai

SO PCT Int. Appl., 20 pp.

CODEN: PIXXD2

DT Patent

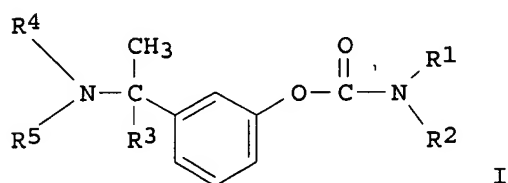
LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003101917	A2	20031211	WO 2003-IN210	20030602
	WO 2003101917	A3	20040812		
	W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,			

LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM,
 PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT,
 TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
 KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
 FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
 BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

IN 2002MU00484 A 20040228 IN 2002-MU484 20020531
 IN 2003MU00166 A 20050204 IN 2003-MU166 20030206
 AU 2003263574 A1 20031219 AU 2003-263574 20030602
 US 2006293518 A1 20061228 US 2006-516104 20060807
 PRAI IN 2002-MU484 A 20020531
 IN 2003-MU166 A 20030206
 WO 2003-IN210 W 20030602
 OS CASREACT 140:27668; MARPAT 140:27668
 GI



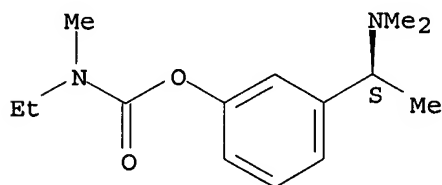
AB Phenylcarbamates [I; R1 = H, (un)branched lower (cyclo)alkyl, cyclohexyl, allyl, propargyl, benzyl; R2 = H, Me, Et, propyl; NR1R2 = three-to-eight-membered ring with or without a hetero atom like nitrogen or oxygen; R3 = H, lower alkyl; R4, R5 = lower alkyl; e.g., racemic rivastigmine] are prepared in high yield and selectivity by the reaction of the corresponding I phenol [e.g., 3-[(1-dimethylamino)ethyl]phenol] with a 4-nitrophenylcarbamate 4-O2NC6H4O2CN(R1)R2 (e.g., 4-nitrophenyl N-ethyl-N-methylcarbamate) in the presence of a base (e.g., potassium carbonate).

IT 123441-03-2P, Rivastigmine
 RL: PUR (Purification or recovery); SPN (Synthetic preparation); PREP (Preparation)
 (process for the preparation of Ph carbamates)

RN 123441-03-2 CAPLUS

CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L10 ANSWER 27 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN

AN 2003:847386 CAPLUS

DN 140:59356

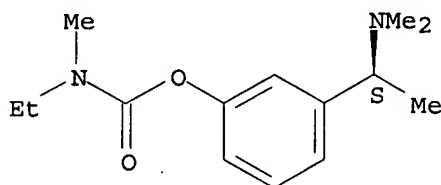
TI Asymmetric, Catalytic Synthesis of α -Chiral Amines Using a Novel Bis(phosphine) Monoxide Chiral Ligand

AU Boezio, Alessandro A.; Pytkowicz, Julien; Cote, Alexandre; Charette, Andre B.

CS Departement de Chimie, Universite de Montreal, Montreal, QC, H3C 3J7, Can.

SO Journal of the American Chemical Society (2003), 125(47), 14260-14261
 CODEN: JACSAT; ISSN: 0002-7863
 PB American Chemical Society
 DT Journal
 LA English
 OS CASREACT 140:59356
 AB It was shown that (R,R)-Me-DuPhos monoxide [BozPHOS; (2R,2'R,5R,5'R)-1,1'-(1,2-phenylene)bis[2,5-dimethylphospholane] 1-oxide] is a very effective ligand in the copper-catalyzed addition of dialkylzinc to N-phosphinoylimines providing access to α -chiral amines. The new ligand is particularly effective for the addition of the lesser reactive dimethylzinc. The major advantages of this process are high yields, broad substrate scope, and high enantioselectivities with low catalyst loading (3 mol %). New compds. thus prepared included N-[(1S)-1-(2-methoxyphenyl)propyl]-P,P-diphenylphosphinic amide, N-[(1S)-1-(2-chlorophenyl)propyl]-P,P-diphenylphosphinic amide, N-[(1S)-1-(2-methylphenyl)propyl]-P,P-diphenylphosphinic amide, N-[(1S)-1-(3-methylphenyl)ethyl]-P,P-diphenylphosphinic amide, N-[(1S)-1-(3-methylphenyl)ethyl]-P,P-diphenylphosphinic amide, N-[(1S)-2-methyl-1-phenylpropyl]-P,P-diphenylphosphinic amide.
 IT 123441-03-2P, (Ethyl)(methyl)carbamic acid 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester
 RL: SPN (Synthetic preparation); PREP (Preparation)
 (rivastigmine; asym., catalytic synthesis of chiral amines via reduction of diphenyl(phenylmethylene)phosphinic amides using (phenylene)bis[2,5-dimethylphospholane] oxide as ligand)
 RN 123441-03-2 CAPLUS
 CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



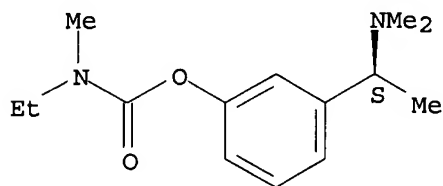
RE.CNT 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 28 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN
 AN 2003:353645 CAPLUS
 DN 140:61086
 TI Pharmaceuticals as antifoulants: concept and principles
 AU Rittschof, Dan; Lai, Chien-Houng; Kok, Lai-Mun; Teo, Serena Lay-Ming
 CS Duke University Marine Laboratory, Nicholas School of the Environment, Beaufort, NC, 28516-9721, USA
 SO Biofouling (2003), 19(Suppl.), 207-212
 CODEN: BFOUEC; ISSN: 0892-7014
 PB Taylor & Francis Ltd.
 DT Journal
 LA English
 AB The hypothesis that pharmaceuticals, with their known syntheses, chemical properties and primary mechanism of action would be an efficient source of new antifouling agents compatible with existing antifouling coating technol. was tested. Twenty-three compds. at concns. from 5 μ g ml⁻¹ to 40 ng ml⁻¹ were tested for toxicity and inhibition of settlement of barnacle larvae. The compds. had a wide range of solubility in water and covered nine primary mechanisms of action in vertebrates. The upper level of potency was chosen because compds. that are highly potent have greater practical potential. The goal was to find compds. with high inhibition of settlement and low toxicity. Of the 23 compds. tested, 22 had significant

effects on barnacle larvae. The variety of chemical structures and their variation in water solubility support the hypothesis that pharmaceuticals that are compatible with existing coatings technol. should be considered as antifouling agents. Moreover, factors such as coating compatibility and environmental fate should be addressed early in the development process.

IT 123441-03-2, Exelon
RL: PAC (Pharmacological activity); PRP (Properties); TEM (Technical or engineered material use); BIOL (Biological study); USES (Uses)
(evaluation of pharmaceuticals as potential antifoulants in marine coatings)
RN 123441-03-2 CAPLUS
CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

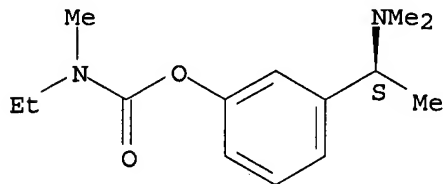


RE.CNT 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 29 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2002:895868 CAPLUS
DN 139:143316
TI ADME evaluation 2. A computer model for the prediction of intestinal absorption in humans
AU Klopman, Gilles; Stefan, Liliana R.; Saiakhov, Roustem D.
CS Department of Chemistry, Case Western Reserve University, Cleveland, OH, 44106, USA
SO European Journal of Pharmaceutical Sciences (2002), 17(4-5), 253-263
CODEN: EPSCED; ISSN: 0928-0987
PB Elsevier Science Ltd.
DT Journal
LA English
AB Purpose: To develop a computational method to rapidly evaluate human intestinal absorption, one of the drug properties included in the term ADME (Absorption, Distribution, Metabolism, Excretion). Poor ADME properties are the most important reason for drug failure in clin. development. Methods: The model developed is based on a modified contribution group method in which the basic parameters are structural descriptors identified by the case program, together with the number of hydrogen bond donors. Results: The human intestinal absorption model is a quant. structure-activity relationship (QSAR) that includes 37 structural descriptors derived from the chemical structures of a data set containing 417 drugs. The model was able to predict the percentage of drug absorbed from the gastrointestinal tract with an r2 of 0.79 and a standard deviation of 12.32% of the compds. from the training set. The standard deviation for an external test set (50 drugs) was 12.34%. Conclusions: The availability of reliable and fast models like the one we propose here to predict ADME/Tox properties could help speed up the process of finding compds. with improved properties, ultimately making the entire drug discovery process shorter and more cost efficient.
IT 123441-03-2, Rivastigmine
RL: PKT (Pharmacokinetics); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(computer model for prediction of intestinal absorption in humans)
RN 123441-03-2 CAPLUS

CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RE.CNT 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 30 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN

AN 2002:645765 CAPLUS

DN 137:194868

TI Pharmacologic treatments of dementia

AU Bonner, Lauren T.; Peskind, Elaine R.

CS Department of Psychiatry and Behavioral Sciences, University of Washington School of Medicine, Seattle, WA, 98108, USA

SO Medical Clinics of North America (2002), 86(3), 657-674

CODEN: MCNAA9; ISSN: 0025-7125

PB W. B. Saunders Co.

DT Journal; General Review

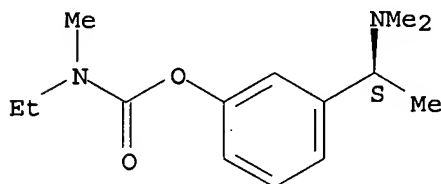
LA English

AB A review. Alzheimer's disease (AD) and other forms of dementia are estimated to affect millions worldwide. Because ests. of the incidence and prevalence of dementia are criteria dependent, the true number of people affected by dementia in the United States is unknown. Is it estimated that AD, the most common cause of dementia, accounts for nearly 70% of dementias. There is still debate about the second and third most common forms of dementia. Recent neuropathol. studies have demonstrated that dementia with Lewy bodies (DLB) may be the second most common cause of dementia, accounting for 15-25% of dementia cases. Other sources consider vascular/multi-infarct dementia (VaD) to be the second most common cause of dementia. Because AD and other forms of dementia are diseases of the aged, prevalence rates should increase as our population continues to age. AD is estimated to affect 4 million Americans. Currently, approx. 5% of Americans aged 65 yr and older suffer from AD, with an estimated 30-50% of Americans aged 85 yr and older suffering from the disorder. By the year 2050, the number of Americans suffering from AD is estimated to rise to 14 million. AD is characterized by a gradual insidious onset of memory loss, global cognitive deterioration, and functional deterioration. Short-term memory is affected early in the course of the illness, reflecting early involvement of the hippocampus and medial temporal lobes. Visuospatial deficits and executive dysfunction also appear early in the illness. Gradually, as the disease process advances, all cognitive functions are impaired. The duration of the illness is 5 to 10 yr, with pneumonia or sepsis as the usual cause of death. The typical findings on neuropathol. examination include hippocampal and neocortical neuritic plaques, neurofibrillary tangles, and neuronal loss. Although there is no cure for AD, two pharmacol. treatment options can provide symptomatic improvement in cognitive and functional deterioration: cholinesterase inhibitors and vitamin E. Cholinesterase inhibitors, which exert their effects by increasing the availability of intrasynaptic acetylcholine, have been demonstrated to be more effective than placebo in the treatment of the cognitive deficits of AD. The antioxidant vitamin E (α -tocopherol) slows functional deterioration in AD. In this article, we review data supporting the use of cholinesterase inhibitors and vitamin E in the treatment of AD and related dementias and present recommendations for incorporating their use into clin. practice. Unless otherwise specified,

when specific effect sizes are described, the efficacy data presented were derived from anal. of observed cases.

IT 123441-03-2, Rivastigmine
RL: ADV (Adverse effect, including toxicity); DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmacol. treatments of dementia patients)
RN 123441-03-2 CAPLUS
CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



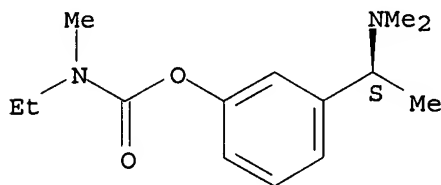
RE.CNT 80 THERE ARE 80 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 31 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2000:899243 CAPLUS
DN 135:86295
TI RBC cholinesterase inhibition: A useful surrogate marker for cholinesterase inhibitor activity in alzheimer disease therapy?
AU Sramek, John J.; Cutler, Neal R.
CS California Clinical Trials, Beverly Hills, CA, 90211, USA
SO Alzheimer Disease and Associated Disorders (2000), 14(4), 216-227
CODEN: ADADE2; ISSN: 0893-0341
PB Lippincott Williams & Wilkins
DT Journal; General Review
LA English
AB A review with 91 refs. Red blood cell (RBC) acetylcholinesterase (AChE) inhibition has been used as a peripheral surrogate marker for the activity of centrally acting AChE inhibitors (AChEIs) in the treatment of Alzheimer disease. As a valid peripheral surrogate marker, RBC AChE inhibition should reflect the central pharmacodynamic activity of the compound and should demonstrate a relation with cognitive or global improvement in patients with Alzheimer disease. As a useful clin. tool, RBC AChE inhibition should also provide an advantage in dose optimization. However, the application of surrogate markers in research and clin. use is controversial (Prentice, 1989; Gotzsche, 1996; Colburn, 1997; De Gruttola et al., 1997). For instance, surrogate markers that have been identified or applied inappropriately can lead to erroneous conclusions, slowing the drug development process (Colburn, 1997). Also, the validation of surrogate markers for the pharmacodynamic activity of central nervous system drugs is not always possible because samples of brain tissue cannot be analyzed in humans. Finally, although validation of peripheral markers for central nervous system drugs has been approached via anal. of cerebrospinal fluid (Cutler et al., 1998a), few markers have been subjected to such rigorous evaluation in clin. studies. The extent to which measures of peripheral AChE inhibition accurately model central drug activity and therapeutic effectiveness of AChEIs, both as individual agents and as a drug class, is the focus of this review. AChEIs comprise a group of structurally diverse compds. with a wide range of relative specificities for the various mol. species of cholinesterase found in plasma, RBCs, and the brain. Studies of RBC AChE inhibition after administration of AChEIs in animals are of limited utility because of the differential sensitivity of AChEIs for human vs. animal forms of AChE, the poor correlation between EDs in animals and humans, and the lack of

standardized measurements of effectiveness. Although clin. studies of donepezil, metrifonate, and eptastigmine have suggested the potential use of RBC AChE inhibition as a predictor of clin. response, the degree of inhibition yielding maximum cognitive improvements was highly variable from compound to compound (30-80%). Further, investigators did not prove a relation between central and peripheral pharmacodynamics or demonstrate an advantage over dose in the ability of RBC AChE inhibition to predict clin. response. A study of rivastigmine in patients with Alzheimer disease revealed that cerebrospinal fluid AChE inhibition correlated well with cognitive performance, whereas peripheral inhibition did not. Therefore, RBC cholinesterase inhibition is not a reliable surrogate marker for the activity of AChEIs as a class of drugs, and its usefulness as a dose optimization tool for individual agents has yet to be demonstrated clearly.

IT 123441-03-2, Rivastigmine
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (RBC cholinesterase inhibition, a useful surrogate marker for cholinesterase inhibitor activity in alzheimer disease therapy i)
 RN 123441-03-2 CAPLUS
 CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RE.CNT 91 THERE ARE 91 CITED REFERENCES AVAILABLE FOR THIS RECORD
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 32 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN
 AN 1999:640694 CAPLUS
 DN 131:276965
 TI Therapeutic system which can be moisture activated
 IN Bracht, Stefan
 PA LTS Lohmann Therapie-Systeme G.m.b.H., Germany
 SO PCT Int. Appl., 49 pp.
 CODEN: PIXXD2
 DT Patent
 LA German
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9949853	A1	19991007	WO 1999-EP1802	19990318
	W: AU, CA, JP, KR, MX, NO, SI, US				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	DE 19814087	A1	19991014	DE 1998-19814087	19980330
	CA 2326662	A1	19991007	CA 1999-2326662	19990318
	CA 2326662	C	20070116		
	AU 9933312	A	19991018	AU 1999-33312	19990318
	EP 1069892	A1	20010124	EP 1999-914523	19990318
	EP 1069892	B1	20020807		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, SI, FI				
	JP 2002509879	T	20020402	JP 2000-540819	19990318
	AT 221774	T	20020815	AT 1999-914523	19990318

PT 1069892	T	20021231	PT 1999-914523	19990318
ES 2182507	T3	20030301	ES 1999-914523	19990318
NO 2000004835	A	20000926	NO 2000-4835	20000926
MX 2000PA09579	A	20020311	MX 2000-PA9579	20000929
US 7175853	B1	20070213	US 2000-647289	20001115
PRAI DE 1998-19814087	A	19980330		
WO 1999-EP1802	W	19990318		

AB A therapeutic system is provided for the temporal and controllable administration of ≥ 1 therapeutically active substance to a human or animal by diffusion through the skin or a mucous membrane. The active substance is initially available in a 1st state (specifically, as a salt) for production and storage; in this state, the active substance is chemical stable and is insufficiently permeable for the skin or a mucous membrane. The active substance is transformed into a 2nd state (an acid or base) at the application site when exposed to moisture; in this state, the active substance can diffuse through the skin or a mucous membrane, and is absorbed into the organism. Transformation of the salt into an acid or base by exposure to water is facilitated by an active agent also contained in the system; this active agent is a solid which reacts in aqueous solution in an acidic or basic manner or is a mixture of such substances. This active agent contains $\geq 5\%$ bound or entrapped water. Thus, the anti-Alzheimer's drug ENA 713 H tartrate 10 and $\text{Na}_2\text{SiO}_3 \cdot 5\text{H}_2\text{O}$ 3 were mixed with a solution of silicone adhesive Bio-PSA Q7-4301 in C_6H_6 . The resulting dispersion was spread on a PET film coated with a dehesive fluoropolymer to a surface d. of 60 g/m² after drying, and laminated with Hostaphen RN film. This laminate released .apprx.15 μg ENA 713/cm²/24 h in permeation expts. with bovine udder skin. compared to .apprx.5 μg /cm² for similar preps. containing anhydrous Na_2SiO_3 or no activator.

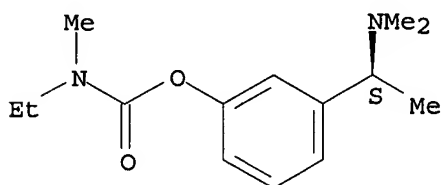
IT 123441-03-2, ENA 713 free base
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(conversion to free base; therapeutic system which can be moisture activated)

RN 123441-03-2 CAPLUS

CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



IT 129101-54-8, ENA 713

RL: RCT (Reactant); RACT (Reactant or reagent)
 (therapeutic system which can be moisture activated)

RN 129101-54-8 CAPLUS

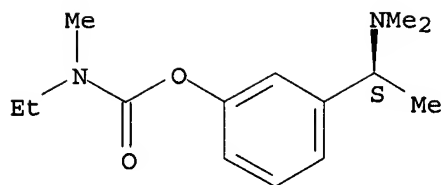
CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl ester, (2R,3R)-2,3-dihydroxybutanedioate (1:1) (CA INDEX NAME)

CM 1

CRN 123441-03-2

CMF C14 H22 N2 O2

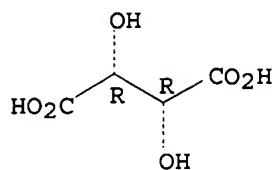
Absolute stereochemistry. Rotation (-).



CM 2

CRN 87-69-4
CMF C4 H6 O6

Absolute stereochemistry.



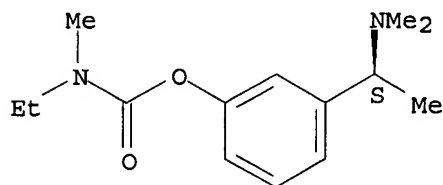
RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 33 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN
AN 1998:601548 CAPLUS
DN 130:55
TI Clinical pharmacology of rivastigmine: a new-generation
acetylcholinesterase inhibitor for the treatment of Alzheimer's disease
AU Polinsky, Ronald J.
CS Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA
SO Clinical Therapeutics (1998), 20(4), 634-647
CODEN: CLTHDG; ISSN: 0149-2918
PB Excerpta Medica
DT Journal; General Review
LA English
AB A review with 25 refs. Rivastigmine (ENA 713, or carbamoylatine) is an
acetylcholinesterase (AChE) inhibitor with brain-region selectivity and a
long duration of action. Both preclin. studies and studies in human
volunteers have shown that rivastigmine induces substantially greater
inhibition of AChE in the central nervous system (CNS) compartment than in
the periphery (40% inhibition of central AChE compared with 10% inhibition
of plasma butylcholinesterase in healthy volunteers). Moreover,
rivastigmine preferentially inhibits the G1 enzymic form of AChE, which
predominates in the brains of patients with Alzheimer's disease (AD).
Evidence from animal studies also suggests that rivastigmine is a more
potent inhibitor of AChE in the cortex and hippocampus, the brain regions
most affected by AD. Absorption of rivastigmine is rapid and almost
complete (>96% of the administered dose). Extensive, saturable first-pass
metabolism, however, leads to bioavailability of approx. 35% of the
administered dose and nonlinear pharmacokinetics. The principal
metabolite of rivastigmine has at least 10-fold lower activity against
AChE compared with the parent drug. Rivastigmine is completely
metabolized; the major route of elimination of the metabolites is renal.
Although patients with AD demonstrate 30% to 50% higher plasma concns. of
rivastigmine and its principal metabolite than do healthy elderly
patients, there is no evidence of drug accumulation, which is consistent
with rivastigmine's short pharmacokinetic half-life. Distribution of
rivastigmine into the CNS is extensive, and inhibition of AChE in the
cerebrospinal fluid is detectable 1.2 h after oral dosing in both healthy

volunteers and patients with AD. Peak activity is reached somewhat more slowly in AD patients than in healthy subjects, and the inhibitory effects have a longer duration (6.0 vs. 2.4 h and 12.0 vs. 8.5 h, resp.). Rivastigmine is inactivated during the process of interacting with and inhibiting AChE, and, in contrast to other AChE inhibitors, the hepatic cytochrome P 450 (CYP-450) system is not involved in the metabolism of rivastigmine. This reduces its propensity to interact with drugs metabolized by specific CYP-450 isoenzymes. Consistent with rivastigmine's pharmacokinetic and pharmacodynamic profiles, Phase II and III trials have demonstrated that the drug is a well-tolerated and effective treatment for AD.

IT 123441-03-2, Rivastigmine
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (clin. pharmacol. of rivastigmine, a new-generation
 acetylcholinesterase inhibitor for treatment of Alzheimer's disease, in
 humans and laboratory animals)
 RN 123441-03-2 CAPLUS
 CN Carbamic acid, N-ethyl-N-methyl-, 3-[(1S)-1-(dimethylamino)ethyl]phenyl
 ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RE.CNT 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> s rivastigmine
 L11 620 RIVASTIGMINE

=> s hydrogentartrate
 L12 52 HYDROGENTARTRATE

=> s L11 and L12
 L13 6 L11 AND L12

=> d L13 1-6 bib abs hitstr

L13 ANSWER 1 OF 6 CAPLUS COPYRIGHT 2007 ACS on STN
 AN 2007:313129 CAPLUS
 TI Synthesis of S-(+)-rivastigmine hydrogentartrate
 AU Feng, Jin; Chen, Wei-min; Sun, Ping-hua
 CS Dep. Med. Chem., Sch. Pharmacy, Jinan Univ., Guangzhou, 510632, Peop. Rep. China
 SO Nanfang Yike Daxue Xuebao (2007), 27(2), 177-180
 CODEN: NYDXAN; ISSN: 1673-4254
 PB Nanfang Yike Daxue Xuebao Bianjibu
 DT Journal
 LA Chinese
 AB Objective: To optimize the synthetic procedure of S-(+)-rivastigmine hydrogentartrate which was known as an agent for the treatment of Alzheimer disease. Methods: S-(+)-rivastigmine hydrogentartrate was synthesized by using 1-(3-hydroxyphenyl)ethanone as the starting material via oximation, reduction and N-methylation to produce the key intermediate 3-1-dimethylaminoethylphenol, which finally reacted with N-ethyl-N-methylcarbamoyl chloride. The enantiomers were resolved with

di(+)-p-toluoyl-D-tartaric acid, and the title compound was prepared by mixing S-rivastigmine base with L-(+)-tartrate. Results: The total yield of S-(+)-rivastigmine hydrogentartrate was 4.17%. Conclusion: The materials in this procedure are all com. available. The reaction conditions are mild and total yield is high.

L13 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2007 ACS on STN
 AN 2005:561746 CAPLUS
 DN 143:77963
 TI Process for the preparation of aminoalkylphenyl carbamates in particular rivastigmine hydrogentartrate
 IN Gaitonde, Abhay; Mangle, Mangesh
 PA Generics UK Limited, UK
 SO Brit. UK Pat. Appl., 13 pp.
 CODEN: BAXXDU

DT Patent
 LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	GB 2409453	A	20050629	GB 2003-29970	20031224
	WO 2005061446	A2	20050707	WO 2004-GB50042	20041217
	WO 2005061446	A3	20060105		
	W:				
	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, SM				
	RW:				
	BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	EP 1697313	A2	20060906	EP 2004-806260	20041217
	R:				
	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK, IS				

PRAI GB 2003-29970 A 20031224
 WO 2004-GB50042 W 20041217

OS CASREACT 143:77963; MARPAT 143:77963

AB Rivastigmine hydrogentartrate is prepared from 3-hydroxyacetophenone in a process which has the advantage of avoiding the preparation of zwitterionic intermediates which are very water soluble and need to be isolated by concentration of aqueous solvent; this process is therefore suited to the industrial-scale manufacture of aminoalkylphenyl carbamates. The large amts. of sulfated ash residues left in the product when prepared by prior-art processes and the use of pyrophoric and reagents such as sodium hydride may be avoided by using the title method.

RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2007 ACS on STN
 AN 2001:300512 CAPLUS
 DN 134:305320
 TI Rivastigmine for the treatment of ocular disorders
 IN Goldblum, David
 PA Novartis Ag, Switz.; Novartis-Erfindungen
 SO PCT Int. Appl., 14 pp.
 CODEN: PIXXD2

DT Patent
 LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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PI	WO 2001028553	A1	20010426	WO 2000-EP10234	20001017
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	US 6534541	B1	20030318	US 2000-686025	20001011
	CA 2384690	A1	20010426	CA 2000-2384690	20001017
	EP 1225890	A1	20020731	EP 2000-992430	20001017
	EP 1225890	B1	20041229		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
	JP 2003512324	T	20030402	JP 2001-531383	20001017
	AU 766001	B2	20031009	AU 2001-28349	20001017
	NZ 518164	A	20031031	NZ 2000-518164	20001017
	AT 285764	T	20050115	AT 2000-992430	20001017
	PT 1225890	T	20050531	PT 2000-992430	20001017
	ES 2234708	T3	20050701	ES 2000-992430	20001017
	US 2003119832	A1	20030626	US 2003-349718	20030123
	US 6835748	B2	20041228		
PRAI	EP 1999-120678	A	19991019		
	US 2000-686025	A3	20001011		
	WO 2000-EP10234	W	20001017		

OS MARPAT 134:305320

AB The present invention is in particular related to the use of
rivastigmine in the manufacture of a medicament for the treatment of
ocular disorders selected from glaucoma, normal tension glaucoma and
neurodegenerative disease conditions of the retina and the optic nerve.

RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2001:247162 CAPLUS
DN 134:271266
TI Oral controlled release formulations containing rivastigmine
IN Shah, Rajen; Khanna, Satish Chandra; Kalb, Oskar; Ogorka, Joerg
PA Novartis Ag, Switz.; Novartis-Erfindungen Verwaltungsgesellschaft M.B.H.
SO PCT Int. Appl., 44 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

PI	WO 2001022944	A1	20010405	WO 2000-EP9455	20000927
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	CA 2379595	A1	20010405	CA 2000-2379595	20000927
	BR 2000014440	A	20020618	BR 2000-14440	20000927
	EP 1216032	A1	20020626	EP 2000-971290	20000927
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
	TR 200200683	T2	20020722	TR 2002-683	20000927

HU 2002002744	A2	20030128	HU 2002-2744	20000927
JP 2003510268	T	20030318	JP 2001-526156	20000927
NZ 517335	A	20031031	NZ 2000-517335	20000927
AU 769646	B2	20040129	AU 2001-10197	20000927
RU 2281758	C2	20060820	RU 2002-109236	20000927
NO 2002001452	A	20020322	NO 2002-1452	20020322
ZA 2002002369	A	20021028	ZA 2002-2369	20020325
US 2006246101	A1	20061102	US 2006-479020	20060630
PRAI GB 1999-23045	A	19990929		
WO 2000-EP9455	W	20000927		
US 2002-89265	B1	20020327		

AB Oral controlled release pharmaceutical compns. capable of releasing a therapeutically ED of a drug, e.g., rivastigmine, are described. Thus, tablets contained rivastigmine hydrogen tartrate 7.2, microcryst cellulose fine powder 25.95, HPMC K100M 18.75, microcryst cellulose granular powder 22.35, Mg stearate 0.375, and highly dispersed SiO₂ 0.375 mg.

RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2007 ACS on STN

AN 2000:127379 CAPLUS

DN 132:274211

TI Inhibitory effect of orally administered donepezil hydrochloride (E2020), a novel treatment for Alzheimer's disease, on cholinesterase activity in rats

AU Kosasa, T.; Kuriya, Y.; Matsui, K.; Yamanishi, Y.

CS Tsukuba Research Laboratories; Eisai, Tsukuba, Ibaraki, Japan

SO European Journal of Pharmacology (2000), 389(2/3), 173-179

CODEN: EJPHAZ; ISSN: 0014-2999

PB Elsevier Science B.V.

DT Journal

LA English

AB Donepezil hydrochloride ((+)-2-[(1-benzylpiperidin-4-yl)methyl]-5,6-dimethoxy-indan-1-one monohydrochloride: E2020: donepezil) is a potent and selective acetylcholinesterase inhibitor developed for the treatment of Alzheimer's disease. The present expts. were designed to compare the inhibitory effects of orally administered donepezil and other cholinesterase inhibitors, tacrine (9-amino-1,2,3,4-tetrahydroacridine hydrochloride), (S)-N-ethyl-3-[(1-dimethyl-amino)ethyl]-N-methyl-phenylcarbamate hydrogentartrate (ENA-713, rivastigmine) and 3-[1-(phenylmethyl)-4-piperidinyl]-1-(2,3,4,5-tetrahydro-1H-1-benzazepin-8-yl)-1-propanone fumarate (TAK-147), on the cholinesterase activity in the brain and plasma of rats. Moreover, in order to validate the cholinesterase inhibition data, we measured the brain and plasma concns. of these drugs. Oral administration of donepezil, tacrine, ENA-713 or TAK-147, caused a dose-dependent inhibition of brain and plasma cholinesterase activities. The ID₅₀ values of these compds. for brain cholinesterase activity were 6.3, 40.5, 7.2 and 26.8 µmol/kg, resp. On the other hand, the ID₅₀ were 170, 9.7 and 51.2 µmol/kg, resp. Thus, the ratios of the ID₅₀ were 1.3 and 1.9, resp. Brain and plasma concns. of donepezil, tacrine and TAK-147 increased dose-dependently. The ratios of the concns. (brain/plasma) of these compds. were 6.1-8.4 for donepezil, 14.5-54.6 for tacrine and 7.0-20.6 for TAK-147. The values of 50% inhibitory concentration of these drugs in the brain were 0.42, 3.5 and 1.1 nmol/g, resp. In contrast, the brain and plasma concns. of ENA-713 at all doses, except the two highest doses, were below the quantification limit. These results suggest that orally administered donepezil satisfactorily penetrates into the brain and inhibits cholinesterase there, and that donepezil is a potent and selective inhibitor of brain cholinesterase in comparison with plasma cholinesterase in vivo.

RE.CNT 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2007 ACS on STN

AN 1999:693076 CAPLUS
 DN 131:332022
 TI Effect of donepezil hydrochloride (E2020) on basal concentration of extracellular acetylcholine in the hippocampus of rats
 AU Kosasa, Takashi; Kuriya, Yuka; Matsui, Kenji; Yamanishi, Yoshiharu
 CS Tsukuba Research Laboratories, Tsukuba, 300-2635, Japan
 SO European Journal of Pharmacology (1999), 380(2/3), 101-107
 CODEN: EJPHAZ; ISSN: 0014-2999
 PB Elsevier Science B.V.
 DT Journal
 LA English
 AB The effects of oral centrally acting acetylcholine esterase (AChE) inhibitors donepezil HCl, tacrine HCl, and ENA-713 (rivastigmine hydrogentartrate) developed for the treatment of Alzheimer disease on the extracellular acetylcholine concns. in the brain hippocampus of rats were evaluated using microdialysis without adding cholinesterase inhibitors to the perfusion solution. We also compared the inhibition of brain AChE and brain concns. of the 3 drugs. Donepezil at 2.5 mg/kg and tacrine at 5 mg/kg had significant effects for >6 h. At these doses, the maximum increases were 499 and 422% of the pretreatment levels and were observed at .apprx.1.5 and .apprx.2 h after administration of donepezil and tacrine, resp. ENA-713 had significant effects at 0.625, 1.25, and 2.5 mg/kg, which lasted for about 1, 2, and 4 h, resp. The maximum increases produced by these doses at .apprx.0.5 h after administration were 190, 346, and 458% of the pretreatment levels, resp. The time courses of brain AChE inhibition with 2.5 mg donepezil/kg, 10 mg tacrine/kg, and 2.5 mg ENA-713/kg were mirror images of the extracellular acetylcholine-increasing action at the same doses. The time courses of brain concns. of the drugs after oral administration of 2.5 mg donepezil/kg and 10 mg tacrine/kg were consistent with the course of brain AChE inhibition at the same doses; there was a linear relation between these parameters. Brain concns. of ENA-713 given at 2.5 mg/kg was below the limit of quantification at all time points measured. Thus, oral administration of donepezil, tacrine, and ENA-713 increases acetylcholine concns. in the synaptic cleft of the brain hippocampus mostly through AChE inhibition. Donepezil has a more potent activity than tacrine and a longer-lasting effect than ENA-713 on the central cholinergic system.
 RE.CNT 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

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---Logging off of STN---

=>

Executing the logoff script...

=> LOG Y

COST IN U.S. DOLLARS	SINCE FILE	TOTAL
	ENTRY	SESSION
FULL ESTIMATED COST	209.03	381.34
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE	TOTAL
	ENTRY	SESSION
CA SUBSCRIBER PRICE	-31.20	-31.20

STN INTERNATIONAL LOGOFF AT 08:36:38 ON 14 DEC 2007